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CONTENTS

SYMPOSIUM ON NUTRITION AND THE KIDNEY

INTRODUCTION
Robert M. Kark 463

THE EFFECTS OF DIET ON RENAL FUNCTION IN HEALTHY MEN
Frederick Sargent and Robert E. Johnson 466

NUTRITIONAL ASPECTS OF ACUTE GLOMERULONEPHRITIS
Hyman J. Zimmerman 482

DIETARY TREATMENT IN ACUTE ANURIA
K. G. Lowe and H. Valtin 486

NUTRITION IN CHRONIC RENAL FAILURE
Arthur J. Merrill 497

NUTRITION AND THE NEPHROTIC SYNDROME IN ADULTS
John R. Squire 509

KALIOPENIC NEPHROPATHY
Jerome W. Conn and Robert D. Johnson 523

RENAL FUNCTION IN SCURVY
L. Eales 529

RENAL LESIONS IN KWASHIORKOR
J. N. P. Davies 539

OBSERVATIONS ON THE RENAL DEFENSE OF BODY COMPOSITION IN CHILDREN
Jack Metcoff 543

CALCIUM AND THE KIDNEY
Daniel S. Kushner 561

EDITORIALS:

A WELL-DESERVED TRIBUTE
S. O. Waife 580

ROBERT R. WILLIAMS: A TRIBUTE
Norman Jolliffe 580

TRIBUTE TO DR. ROBERT R. WILLIAMS
William H. Sebrell 582

NUTRITION NEWS 585

NUTRITION BRIEFS 586

NUTRITIONAL QUOTES 587

REVIEWS OF RECENT BOOKS 589

ABSTRACTS OF CURRENT LITERATURE: Niacin Requirements and Metabolism; Nutritional Problems Involving the Gastrointestinal Tract 591

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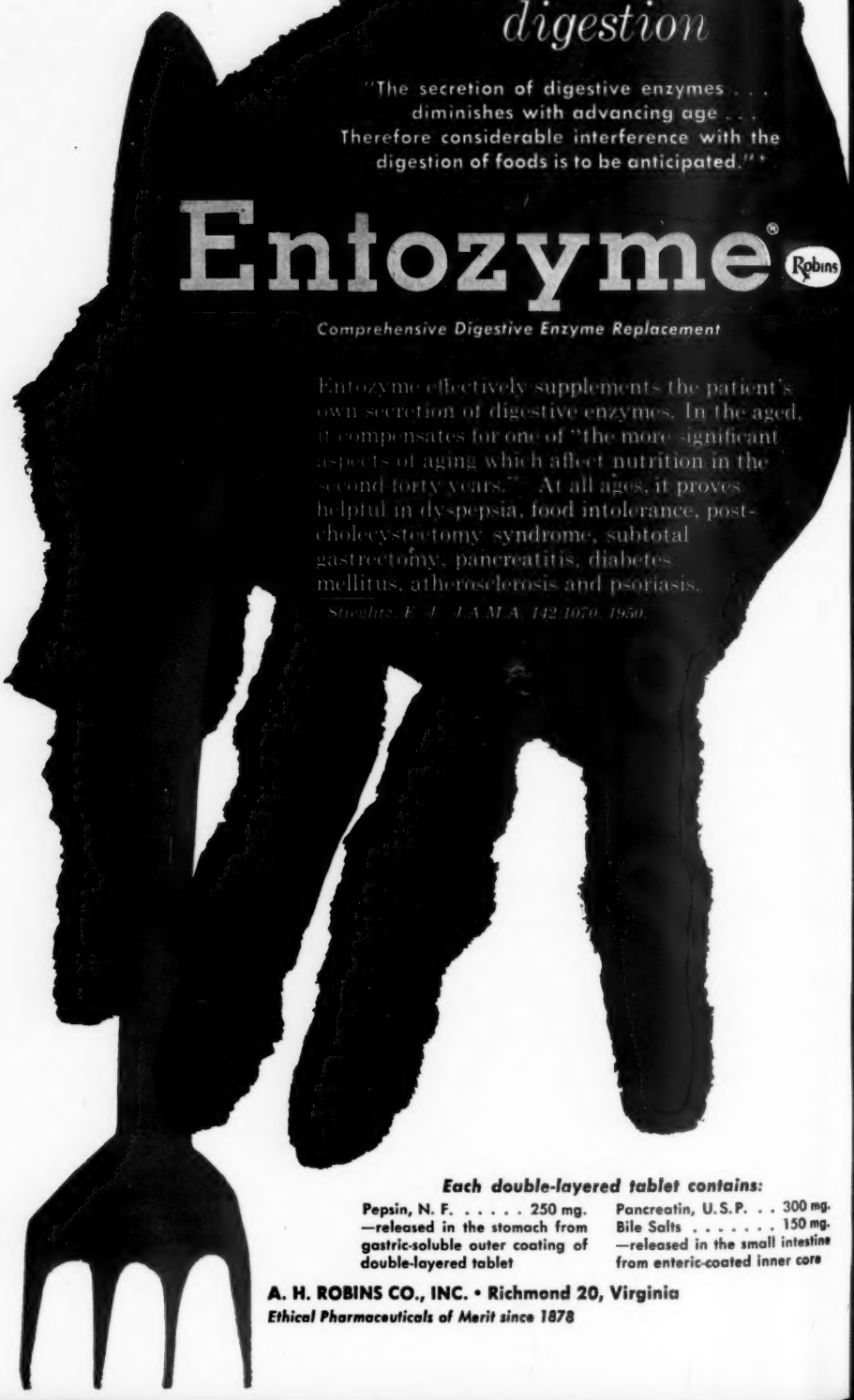

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THE AMERICAN JOURNAL OF Clinical Nutrition

SEPTEMBER-OCTOBER 1956 VOLUME 4, NUMBER 5

Symposium on

Nutrition and the Kidney

Some of us who enjoy the piquant flavor of broiled kidneys wrapped in bacon—and other dishes made with this organ—have learned that they are rich in protein, thiamine, vitamin B_{12}, and other important nutrients. The reasons for this are obvious, for the kidneys—besides controlling the homeostasis of the *milieu intérieur*—are second only to the liver in synthetic activities and in other biochemical functions which serve the body. The kidneys also have an endocrine function, and their wealth of enzymes serve a variety of structures and cells. Despite their need for protein and nutrients to carry on the metabolic activities described above, these small organs seem to be relatively resistant to the effects of nutritional deprivation. Approximately 3600 liters of blood course through the renal vessels each 24 hours, and the kidneys are in the unique position of being able to tap for their exclusive use one-sixth of the nutrients which are pumped around the body each day by the heart. Whether this is the reason for their immunity to nutritional bankruptcy is, of course, speculative.

In animals, disturbances of renal function and structure have been produced with some difficulty by dietary manipulations. Nocturia, hematuria, renal calculi, and tubular abnormalities have developed as a result of inadequate food intake. Thus far, deficiencies of ascorbic acid, vitamin K, vitamin A, alpha-tocopherol, linoleic acid, choline, potassium, magnesium, and chlorine have been shown to affect the kidneys of animals—usually the tubules.[1] The pathologic changes have not always been clear-cut, and this is perhaps due to present-day difficulties in interpreting structural abnormalities in tubular cells by tinctorial techniques. In man, scurvy[2] and hemorrhagic hypoprothrombinemia[3] are the only deficiency states known to produce hematuria, and until recently there was no evidence to hand that deficiencies of other nutrients seriously affected renal function or structure. On the other hand, diseases of the kidney—be they congenital[4] or acquired—are notorious for the frequency with which they compromise the nutrition of the body.

The symposium on *Nutrition and the Kidney* in this issue of the American Journal of Clinical Nutrition deals in the main with methods of protection of the body from the nutritional ravages of kidney disease. An international panel of physicians—whom we hasten to greet—give practical

advice, but they also indicate that the kidney of man may not be as protected from the ill effects of malnutrition as we have suspected. Drs. Sargent and Johnson call attention to alterations of renal function in man produced by changing the proportions of nutrients in the diet. Dr. Conn gives us a new and useful name—"kaliopenic nephropathy"—for the recently described and sometimes serious renal disease produced by potassium deficiency. And Dr. Davies from Central Africa indicates that renal tubular degeneration and isosthenuria are found in some infants ill with kwashiorkor (tropical protein malnutrition). Davies' observation may have some bearing on the etiology of lipoid nephrosis in children and of a recently described abnormality in adults ill with the nephrotic syndrome.[5] In both of these conditions—as in kwashiorkor—tubular degeneration seems to be the outstanding renal abnormality.

The usual forms of glomerulonephritis are probably the result of streptococcus infection. But two afflictions of man which involve the kidneys may be the result of a disturbance of nutrition: these are diabetic nephropathy and certain forms of hypertension, such as eclampsia and essential hypertension.

It has long been suspected that an excessive intake of common table salt was a factor in the production of eclampsia and other forms of hypertension. The relationships between sodium intake and the kidney have been explored recently by Meneely *et al.*,[6] who have produced renal lesions and hypertension in rats by diets containing large amounts of salt; and also by Hartroft and Hartroft,[7] who—in a most important communication—have demonstrated interrelationships between levels of dietary salt, the activity of the juxtaglomerular apparatus of the kidney, and the glomerulosa (aldosterone-producing) layer of the adrenal cortex. The empirical use of diets low in salt in pre-eclampsia and eclampsia and in essential hypertension may eventually be placed on a sound basis by the observations cited above.

Best and Hartroft[8] have produced hypertension and renal disease in adult rats by an acute deprivation of choline during their infancy, the rats being fed at a luxus level during the rest of their life span. This observation, coupled with Hartroft's finding of intercapillary glomerulosclerosis-like deposits in the glomeruli of choline-deficient rats,[9] raises again the question of the nutritional causation of the vascular complications of diabetes, long suspected of being dietary in origin. More exciting, perhaps, in this regard are the recent observations of Brontë-Stewart *et al.*,[10] indicating that a high dietary intake of saturated or hard fat raises blood cholesterol levels in man, while a large intake of unsaturated fatty acids can reduce these. It is interesting to recall the investigations of Burr and his associates[11–13] on linoleic acid deficiency and renal lesions in rats and to speculate that a high intake of hard fats—forced on us in recent decades by the food industry—may have produced hardening of the arteries not only in the kidney of the diabetic patients, but elsewhere in their bodies.

It should be obvious to the reader that a great deal needs to be learned about the effects of malnutrition on the function of the kidney. We hope that the symposium in this issue of the AMERICAN JOURNAL OF CLINICAL NUTRITION will stimulate work in this field.

ROBERT M. KARK, M.D., F.R.C.P., F.A.C.P.

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The Effects of Diet on Renal Function In Healthy Men

By Frederick Sargent II, M.D.,* and Robert E. Johnson, M.D.†

Many alterations can be provoked in the renal function of healthy men by nutritional imbalance, caloric deficit, dehydration, physical work, and extremes of temperature. Frequently the alterations are so large as to be reminiscent of renal disease. This fact strongly supports the belief that it is highly desirable to study the patient under conditions where diet, water intake, work, and temperature are carefully controlled. If this is impossible, then it is essential that the patient's past history with respect to these variables be determined and taken into account in evaluating the results of tests of renal function. Conversely, the experimental human physiologist will find that some aspects of renal physiology can be illuminated by studies involving nutritional and environmental alterations.

The general aim of this paper is to present changes which we have observed in healthy men whose renal function has been studied by standard clinical methods, as well as by some quantitative techniques which are not yet applied routinely and universally. Our observations included the qualitative measurement of glycosuria, ketonuria, and albuminuria; quantitative study of excretion of formed elements; quantitative measurement of serum nitrogenous constituents, and clearances of creatinine and electrolytes; and finally, studies of regulation of total body water and some aspects of water diuresis.

Our conclusions are based on functional deviations from the "normal limits," a statistical concept which we have been able to define more sharply than is generally possible under clinical conditions. Over a period of four years we have studied a total of 211 subjects under strict continuous control of diet, fluid intake, and daily activity for a total of 8698 man-days. During 3097 man-days the subjects were living on entirely adequate diets with unlimited fluid available and engaging in only moderate daily activity. Data collected during these periods provided the "normal limits" to which we refer.

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* Associate Professor of Physiology, University of Illinois, Urbana.

† Professor and Head of Department of Physiology, University of Illinois, Urbana.

MATERIALS AND METHODS

The present paper will deal with a small portion of observations made during three major studies. These studies were designed to assess the effects of different nutrient regimens on the functions of important organs and systems of young men exposed to three environmental conditions: temperate surroundings, moderate cold, and heat (Table I). A large battery of tests was conducted, including measurement of nutrient balances, and liver, kidney, cardiovascular, and endocrine function. Here, however, we shall deal only with observations bearing on the functioning of the kidney and a few of its relations to water balance. All experimental protocols in the three studies were identical, as were all the laboratory methods. However, according to this plan, the environments in which the subjects worked were different: temperate conditions in 1953, moderate cold in 1954, and humid heat in 1955 (Table I). By force of circumstances, different subjects had to be used in each of the three tests. In 1953, eight university student volunteers were employed, in 1954, 99 volunteer airmen, and in 1955, 99 volunteer airmen (Table I). All subjects were young males who had been judged fit for these studies

after a comprehensive medical examination. None had demonstrable renal disease.

Twenty different nutrient regimens were investigated (Table II). Water intake was either unrestricted or limited to 900 ml/day. Caloric intakes per day were set at 0, 1000, 2000, or 3000. The percentage of calories provided from protein was set at 0, 2, 15, or 30; the percentage of calories provided from carbohydrate, 0, 20, 52, or 100; and the percentage provided from fat, 0, 33, 70, or 78. All these regimens were supplemented with a luxus supply of vitamins. In Table II the code presents the information for any given regimen for percentage calories from protein, carbohydrate, and fat calories per day, and for water intake. For instance, "15/52/33 1000 L" was a regimen which provided 1000 calories, the percentage distribution of which was 15 protein, 52 carbohydrate, and 33 fat, with 900 ml of fluids (L—limited) per day. The same regimen U (U—unlimited) would permit the subject to drink *ad libitum*. "Control" subjects subsisted at all times on an abundant diet of fresh and frozen food with unrestricted water.

The evaluation of the experimental regimens was accomplished by a set protocol consisting of two weeks of pre-experimental period (PRE), two weeks of experimental period (EXP), and two weeks of recovery period (REC). During the pre-period all subjects subsisted on an adequate diet providing sufficient calories to maintain the body weight without restriction of water intake. They all lived in comfortable rooms and performed only moderate physical work. Experimental periods involved subsistence on one or another of the nutrient regimens shown in Table II. In the "cold" study and the "hot" study, but not in the "temperate" study, all subjects moved into simulated survival conditions (see Table I) in the field where they were provided with adequate environmental protection. Half of them worked hard—marching 12 miles per day—and half of them performed light work—marching 3 miles per day. Recovery periods

TABLE I

Environmental temperatures during experimental periods and subjects studied in survival ration investigations, 1953-1955

Date	Mean environmental temperature, °F			Subjects		Age, years		% Negro subjects
	Maximum	*Minimum*	*Mean*	*Groups*	*No.*	*Mean*	*Range*	
Jan.–June 1953	----	----	75-80 *	1T	8	23	20-26	12.5
Feb.–Apr. 1954	42	18	30	1C	22	18	17-20	27.2
				2C	22	18	17-20	68.2
				3C	22	18	17-22	13.6
				4C	21	18	17-20	100.0
				5C	12	28	21-41	0.0
June–July 1955	94	67	80	1H	22	18	17-21	27.2
				2H	22	18	17-21	22.7
				3H	22	19	17-27	22.7
				4H	22	18	17-21	27.2
				5H	11	18	17-21	36.4

* *Spent majority of time in heated buildings.*

involved rehabilitation diets in which caloric and water intake were not limited. The subjects moved back into their comfortable quarters.

into the experimental design gave special attention to various kinds of control. First, nonspecific, situational, and environmental variables were accounted for by subjects whose

TABLE II

Man-days of subsistence on nutrient regimens studied

Nutritional regimen		Temperate		Cold		Hot	
		*Moderate**	*Hard*	*Moderate*	*Hard*	*Moderate*	*Hard*
PRE		336	---	1394	---	1367	---
ST 0	U	37	---	30	33	45	25
	L	40	---	31	48	30	36
0/100/0	U	26	---	28	28	18	17
1000	L	26	---	28	28	18	18
0/100/0	U	26	---	28	24	24	18
2000	L	28	---	28	28	12	18
2/20/78	U	14	---	28	28	9	16
1000	L	14	---	28	28	18	18
2/20/78	U	14	---	34	24	18	16
2000	L	9	---	28	28	18	18
15/52/33	U	24	---	28	28	18	18
1000	L	24	---	28	28	18	9
15/52/33	U	36	---	28	28	18	17
2000	L	15	---	28	28	18	11
15/52/33	U	65	---	28	28	18	18
3000	L	47	---	28	28	8	18
30/0/70	U	14	---	28	28	9	18
1000	L	7	---	28	28	18	14
30/0/70	U	14	---	28	28	18	18
2000	L	14	---	28	28	11	18
Control	U	----	---	84	84	99	---
REC		340	---	1428	---	1201	---
Total		1170		4138		3390	
		8698					

* *"Moderate" and "Hard" designate degree of activity.*

In all periods food intake was measured quantitatively and there was a continuous quantitative collection of urine and feces. Various clinical, physiologic, and biochemical tests were conducted once a week on each subject. All methods employed were standard and will be identified in the appropriate sections to follow.

The statistical considerations which went

diet was abundant in all respects throughout. Second, individual idiosyncrasy was accounted for by pre-, experimental, and recovery period comparisons for individual subjects. Third, paired feeding technique contributed evidence on the separate effects of work, water intake, caloric intake, and caloric distribution among protein, carbohydrate, and fat. Finally, since methodology was standardized, the three

studies taken together allow conclusions to be drawn concerning the effects of the environment. The conclusions from the data have been tested mainly by Fisher's "t" test and the Chi-Square test.[1]

by hard work. Exposure to extreme cold, regardless of diet, will produce ketonuria, whereas life in hot climates seems not to predispose to ketonuria.[3]

In the present studies ketonuria sometimes

TABLE III

Ketonuria in urine collected under standard conditions of rest and recumbency: Pre-period data

Environmental condition	Total no. tested	No. specimens showing given reaction					
		0	*tr*	*+1*	*+2*	*+3*	*+4*
Temperate (1953)	146	146	0	0	0	0	0
Moderate cold (1954)							
1. Experimental subjects	158	116	18	15	4	3	2
2. Control subjects	22	13	3	3	2	0	1*
Moist heat (1955)							
1. Experimental subjects	170	169	1	0	0	0	0
2. Control subjects	23	23	0	0	0	0	0

**Acute respiratory infection on day of test.*

QUALITATIVE TESTS

Reaction

Diets which are acid in ash or ketogenic often drive the urinary pH down as low as 5.5 (Hydrion Papers®) and the titratable acidity[2] as high as 50 meq/day. By contrast, diets of alkaline ash often drive the urinary pH as high as 8.0. In such specimens the titratable acidity is zero by definition.

Glycosuria

Glycosuria in healthy men is extremely rare; a strongly positive reaction can be a very significant finding. In approximately 1600 qualitative tests (Clinitest® tablets) positive tests were obtained only five times, and none of these was over one plus regardless of environmental exposure or extreme nutritional imbalance.

Ketonuria (Rothera Reaction)

Unlike glycosuria, ketonuria of significant degree is easily produced in healthy subjects by nutritional imbalance or exposure to cold, or

appeared during brief exposure to moderate cold even when all subjects were subsisting on an adequate balanced diet (Table III). By contrast, temperate conditions and moist heat, under identical circumstances, did not predispose to ketonuria. Therefore, the conclusions reached by Sargent and Consolazio[3] are confirmed and extended.

Another general condition which produces ketonuria in healthy men is hard work followed by a period of rest without food.[3] Two points of some differential interest are that (1) this type of ketonuria can be observed in well-fed individuals provided they do not eat after the exercise, and (2) the ketonuria always disappears after food is eaten. Table IV is adapted from a report by Johnson[4] and illustrates this kind of ketonuria.

Caloric deficits, when extreme enough, will regularly evoke ketonuria. Among 40 subjects who starved for periods ranging from seven to fourteen days, reactions of +4 were almost invariable. Decreasing the caloric

TABLE IV

Post-exercise ketonuria (After Johnson, 1943)

Subjects and conditions	Ketonuria
14 marathon runners after race (Spring)	All showed from +1 to +4
16 soldiers after marching in desert (Summer)	Majority showed from +1 to +4
17 soldiers after marching at 100°F for 2 hours	14 showed from +1 to +4
6 laboratory workers after marching 10 miles (Cool day)	All showed from +1 to +3, changing to 0 after eating a meal

deficit moderates the ketonuria except when the nutrient intake is predominantly from fat. When caloric deficits of the order of 1000 cal/man/day were imposed on 24 subjects who were receiving 2000 cal/day of pure carbohydrate, no ketonuria was observed in two weeks. On the other hand, when the caloric deficit and intake were the same as before, a diet providing 70 per cent of the calories from fat and 30 per cent from protein invariably caused marked ketonuria. In view of the extreme rarity of glycosuria in normal young individuals, a finding of glycosuria with ketonuria must be regarded as definitely abnormal.

Albuminuria (Sulfosalicylic Acid Test)

In our healthy young subjects urine was collected under standard conditions of rest and recumbency, and albuminuria which persisted from week to week did not occur. This experience is substantiated by the report of Wolman.[5] However, transient albuminuria, up to four plus, was quite common after marching one hour at 3.75 m.p.h. (Table V). Vigorous exercise such as running very commonly produces albuminuria.[4,6] On the other hand, under conditions of rest and recumbency, albuminuria may occur when the subject has been subsisting on an unbalanced diet (Table VI). Exposure to cold accentuates this phenomenon and even precipitates albuminuria among young men on adequate balanced regimens (Table VI). "Cold" albuminuria has been observed by other investigators and has been produced under experimentally controlled conditions.[7,8]

Morphology

When an accurately timed urinary specimen is collected under standard conditions of rest and recumbency and the frequency of formed elements is assessed according to the concepts of Addis,[9] it can be shown that microscopic

TABLE V

Effect of moderate exercise on albuminuria (Summer, 1955)

Period	Resting		Exercise		Post-exercise	
	Number tested	*Number positive*	*Number tested*	*Number positive*	*Number tested*	*Number positive*
PRE I	97	0	97	5	97	0
PRE II	96	0	93	7	94	0
EXP I	92	0	86	4	90	0
EXP II	91	4	0	---	0	---
REC I	87	0	80	13	81	2
REC II	90	0	88	9	89	3
Total	553	4	444	38	451	5
%		*0.7*		*8.6*		*1.1*

hematuria and cylindruria may occur in healthy male subjects. Among the variables which we have studied, dietary imbalance is far more conducive to cylindruria and hematuria than are exposure to environmental heat and cold, physical work amounting to 290 cal/-hr, or chronic dehydration of two weeks' duration. With great regularity, starvation for two weeks or a dietary regimen consisting of pure carbohydrate will be accompanied by a urinary excretion of as many as 250,000 casts per hour and 50,000 red blood cells per hour. Although the great majority of the casts are hyaline casts, a few granular types may be seen. On occasion, unbalanced diets high in fat will also provoke microscopic hematuria and cylindruria. Balanced diets, even when fed so as to produce caloric deficits of 2000 cal/-day, very rarely produce such changes in urinary sediment. Although the physiologic mechanism of this phenomenon is not evident, the cylindruria and hematuria regularly disappear during rehabilitation from such regimens.

When a subject is predisposed by an unbalanced diet, then the microscopic hematuria and cylindruria may be accentuated by moderate work such as marching for one hour at 3.75 m.p.h. Even among well-fed subjects violent exercise, such as running, will produce in a majority microscopic hematuria and cylindruria.[4] Under these conditions granular and cellular casts may predominate.

When the white blood cells and epithelial cells in the urine are studied quantitatively, the predominant findings are (1) tremendous individual variability, and (2) lack of correlation with any of the dietary and environmental variables studied. After an hour of moderate work, the rate of excretion of these cells tends to become smaller.

TABLE VI

Albuminuria in urine collected under standard conditions of rest and recumbency: Pre- and experimental periods

Environmental condition	Pre-period		Experimental period	
	Number tested	*% positive*	*Number tested*	*% positive*
Temperate (1953)	48	0.0	85	0.0
Moderate cold (1954)				
1. Experimental subjects	174	0.6	169	37.3
2. Control subjects	23	0.0	24	54.2
Moist heat (1955)				
1 Experimental subjects	170	0.0	161	2.5
2 Control subjects	23	0.0	22	0.0

QUANTITATIVE FUNCTIONAL TESTS

We have systematically studied renal function by currently popular clinical tests. Striking functional changes, in some cases approaching pathologic values, may be produced by nutritional imbalances or deficiencies. The standard conditions of rest and recumbency which we have employed in all studies of renal function need defining. Twenty-five men at a time are customarily studied. They come, postabsorptive, to a comfortable room and recline quietly for one hour. During this hour body temperature, pulse rate, and respirations are counted. At the end of the hour they void and each drinks 100 ml of water; then they lie down again. This is time "zero". At the end of exactly 120 minutes the subjects void again into special containers. This urinary specimen is used for all tests of renal function. At time 60 minutes a sample of venous blood is drawn (with minimal stasis) for chemical analysis and hematology. During the 120-minute period, lying and standing blood pressure are measured and an electrocardiogram is taken. During this interval the subjects are not permitted to smoke, eat, or drink; and they are comfortably recumbent except on the three occasions when they are required to move about for a brief period.

Serum Urea, Nonprotein Nitrogen, and Creatinine

A combination of chronic dehydration and a diet which contains over 12 g of nitrogen per day invariably raises the concentrations of urea, nonprotein nitrogen, and creatinine in the blood. Values of 40–50 mg/100 ml of serum urea nitrogen are common. These high values may be prevented or ameliorated by an adequate water intake or a low protein diet.

Creatinine and Urea Clearance

Endogenous creatinine clearance[10,11] diminishes during caloric deficiencies independently of the percentage of calories from protein, carbohydrate, and fat (Fig. 1). In starvation, values as low as 40 per cent of the normal for that subject may be observed. For any given nutrient regimen a greater diminution will be found with intakes of 1000 cal/day than with 2000 cal/day. In contrast to its effect on serum nitrogenous values, chronic dehydration does not significantly alter the creatinine clearance. In contrast, acute dehydration may markedly

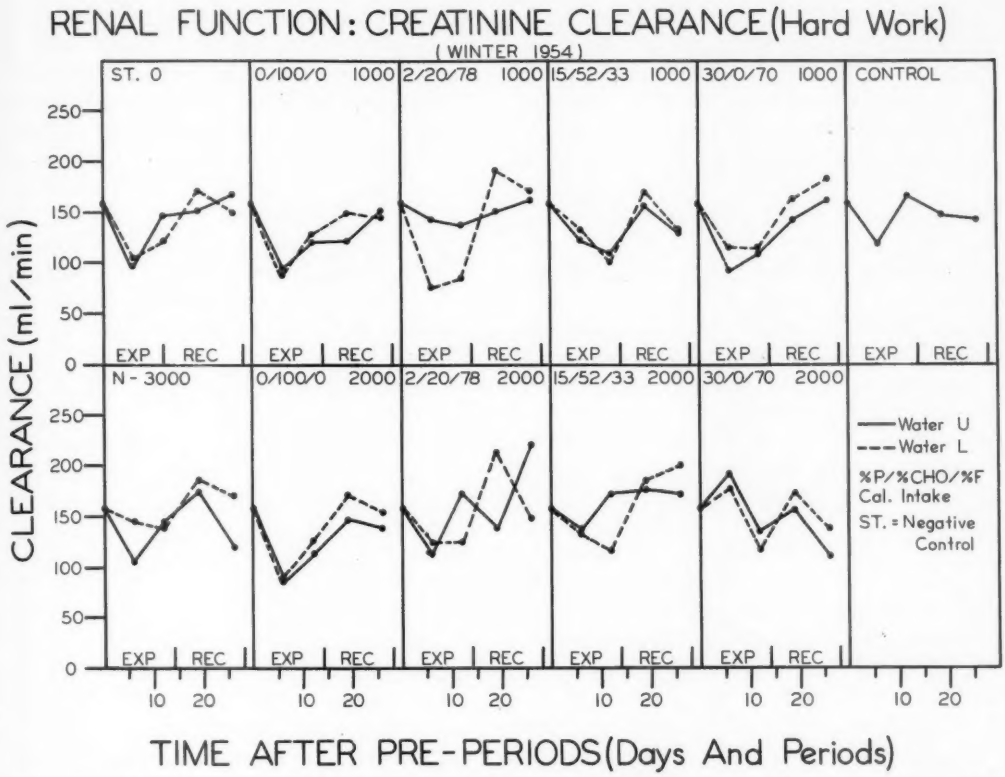

Fig. 1. Renal function: "creatinine" clearance. N – 3000 = 15/52/33 3000. Pre-period clearance is mean clearance for all subjects during the two tests of that period (see text).

reduce creatinine[12] and mannitol clearances.[13] When the nitrogen intake is high, the values for creatinine clearance tend to be somewhat erratic. This variability has been reported by several other workers.[14,15,16] Changes in urea clearance comparable to those shown in Figure 1 have been reported by other investigators, notably McCance and Widdowson,[17] during periods of combined sodium depletion, caloric deficit, and moderate protein intake.

Osmotic Clearance

If the concept of clearance is applied to electrolytes and total osmotically active substances, gross variations in diet will produce large alterations in the numerical values of the clearances. For instance, in a group of 16 male subjects after two weeks of a diet consisting of pure carbohydrate, the mean value for osmotic clearance had diminished to approximately 20 per cent of normal and the values for sodium and chloride clearances were zero.

Comment

One must interpret the mathematical clearance value with caution and with full knowledge of the patient's dietary history. Variations in dietary intake may be accompanied by alterations in serum concentration and in urine concentration; usually changes in the urinary value are proportionately considerably greater than changes in the serum. As a consequence the apparent clearance of either organic or inorganic substances can exhibit a marked decrease when the equation $C = UV/P$ is used. It is still unsettled whether such gross changes in clearance are of any pathologic significance.

WATER RETENTION AND OSMOTIC DEPLETION

Using the concepts popularized by many

investigators such as Bull,[18] the kidney may be regarded fundamentally as an organ for regulating body water and osmotically active materials. The currently accepted theories[19] involve a homeostasis, the essential features of which are central osmoreceptors which control the secretion of antidiuretic hormone, which in turn regulates facultative reabsorption of water by the renal tubule.

One plan of our rather elaborate nutritional studies was to clarify systematically and quantitatively the water economy in healthy subjects when experimentally exposed to all possible combinations of (a) water deprivation, (b) salt deprivation, and (c) protein deprivation. These experimental conditions, therefore, produced the three commonly recognized varieties of hydropenia: i.e., pure water depletion, salt depletion hydropenia, and mixed salt and water depletion hydropenia.[20] In addition, two other rather uncommon kinds of dehydration were studied. The first was hydropenia in which protein intake was high but salt intake low. The second was severe voluntary dehydration[21] by subjects whose total osmotically active intake was low; these latter subjects were permitted water in unlimited quantities, but were not thirsty, and developed a hyposmotic hydropenia.

From these studies a comprehensive quantitative expression for the interdependence among diet, total body water, and osmotic relations in the body, can be made. The mathematical generalization involves four variables (1) O, the total osmotic content of the body; (2) V, the total body water; (3) C, the normal total body osmotic concentration, which is O/V; and (4) R, the per cent net recovery in four hours of a water load equal to 2 per cent of the body weight.

When water is limited, but a high osmotic load is imposed by the dietary regimen, the situation can be expressed as follows:

$$O/V \text{ becomes } \frac{O_1}{(V - \Delta V)} = C_1$$

where O_1 is the total body osmotic content after dehydration and C_1 is the body osmotic concentration after dehydration. In this type of dehydration, water is lost (ΔV) and O remains constant, or is increased by dietary intake and becomes O_1. A water load would cause a diuresis only in so far as it was greater than ΔV, or would cause $O_1/(V - \Delta V)$ to decrease below C. Since ΔV is the limiting quantity, added water would be retained under the conditions of our experiment, in which the water test dose was less than ΔV.

When dehydration is provoked by limitation of water during regimens of low osmotic load (e.g., in the pure carbohydrate regimen) the situation can be expressed as follows:

$$O/V \text{ becomes } \frac{(O - \Delta O)}{(V - \Delta V)} = C_2$$

where C_2 is the total body osmotic concentration after dehydration. In this kind of dehydration both O and V decrease, O because the diet s low in salt and protein, and V because of water restriction. Therefore, C_2 depends upon the relative magnitude of ΔO and ΔV. If after dehydration C_2 were equal to or less than C, an increase in the denominator by addition of water would resu t in the excretion of the added water to reduce the ratio $(O - \Delta O)/(V - \Delta V)$ in an attempt to protect C.

In the normally hydrated and well-fed subject the water test dose would tend to increase V and reduce O/V and the test dose of water would be excreted.

The experimental data were obtained by the use of the following methods: Body water was determined directly as deuterium oxide space. Oral dosage was employed and urinary D_2O/H_2O ratios were used for calculation.[22] Osmotic measurements of serum and urine were made either with a conventional freezing point depression thermometer or with a thermistor device (Fiske Osmometer). The water diuresis test was a modification of that of Robinson, Power, and Kepler.[23] No food or water was allowed after the evening meal on the day prior to the test. On the morning of the test day the subjects reclined for a basal period of 90 minutes before the test began and remained reclining thereafter, except for periods during which specimens were collected. At 8:00 a.m. the test began with the subjects emptying their bladder as completely as possible; between 8:00 and 8:45 a.m. the subjects drank a water

load which was equal to 2 per cent of their body weight; at precisely 9:00, 10:00, 11:00 and 12:00 o'clock each subject emptied his bladder as completely as possible. During all tests the subjects were postabsorptive when the test began and were not allowed to smoke, eat, or drink. The five specimens of urine were measured, basal excretion was calculated, and sum of sodium and potassium intake. Hence the concept of "osmotic depletion" can be used as implying a negative balance with respect to both nitrogen and electrolytes.

When water intake was unlimited for two weeks, the water test dose was in large part excreted during the four hours of the test, and body water as measured by deuterium oxide

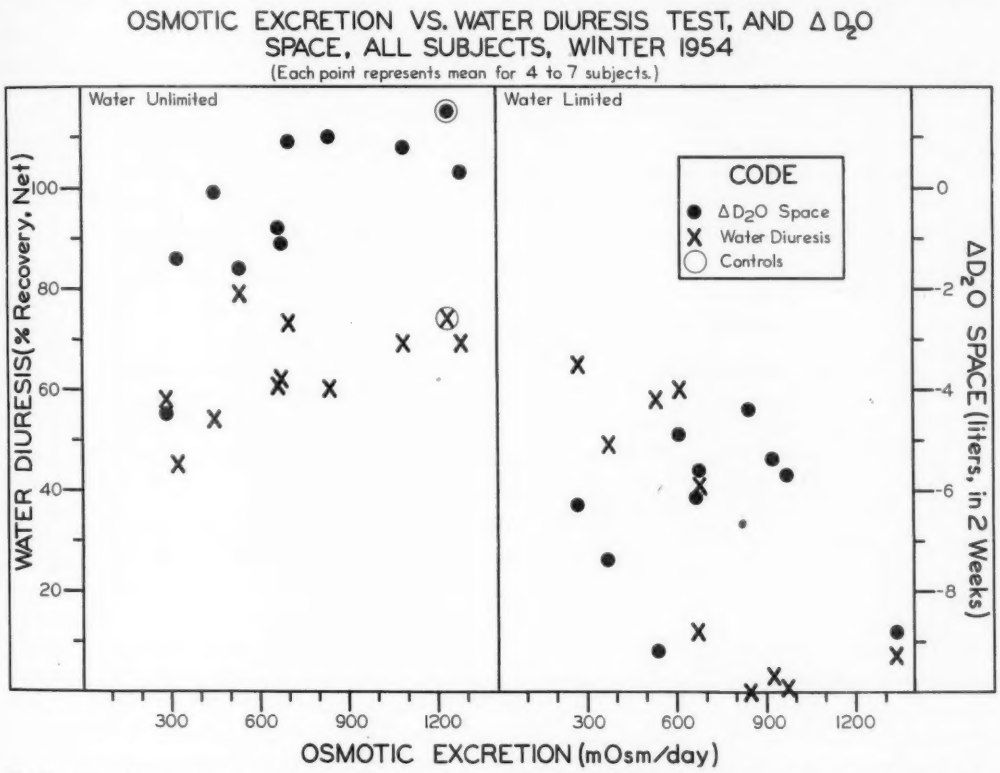

Fig. 2. Osmotic excretion and water diuresis test, and ΔD_2O space. Each point represents mean for 4 to 7 subjects after two weeks of controlled, restricted dietary regimen.

results were expressed as net recovery of the test dose, corrected for basal excretion.

Nutrient balances were calculated from intake as measured by chemical analysis and output in urine and feces; where appropriate, output also included dermal and pulmonary losses. Osmotic balance is complicated by the endogenous production of osmotically active material which is excreted in the urine. However, a very close correlation exists between daily urinary osmolar excretion and the sum of protein intake calculated as urea and twice the remained substantially normal, the controls representing the ideal situation (Fig. 2). With decreasing osmotic excretion, there was a tendency toward some decrease in both the recovery of the water test dose and in the body water. When water intake had been limited to 910 ml daily for two weeks, there was an average decrease in body water of as much as nine liters, and no apparent correlation with osmotic load. On the other hand, recovery of the water test dose was definitely correlated with osmotic load. For osmotic

excretions above 700 milliosmols per day, the water test dose was retained in dehydrated subjects. For osmotic excretions below 650 milliosmols per day, the test dose was excreted as much by chronically dehydrated as by fully hydrated subjects. That is to say, the osmotically depleted subjects did not retain water even when chronically dehydrated, whereas the subjects who were not osmotically depleted did retain water when chronically dehydrated. Urinary volumes for the following 16 hours showed no changes indicative of a delayed diuresis in those subjects who retained the test dose.

Data for the net recovery in the water diuresis test can be fitted satisfactorily by simple equations. In the unlimited water groups, a straight line can be plotted according to the regression equation:

$$R = 0.025x + 49$$

where x is urinary osmotic excretion.

The diminution of net recovery of the water test dose has been observed by other investigators using low osmotic diets.[24] Our interpretation is based on the facts that such subjects are not thirsty and that they dehydrated themselves voluntarily to the extent of as much as 400 ml/day. Therefore, their osmotic relations may be such as to lead to retention of some of the test dose.

In the limited water groups, a sigmoid relationship holds in the form

$$R = -a(x-b)^{1/n} + c$$

where: R is per cent recovery of the test dose; a is related to the percentage recovery for very low osmotic excretion; b is the osmotic excretion at the point of maximum slope; n is a constant related to the rapidity with which the curve falls off between the two points of inflexion; and x is the osmotic excretion. This set of data can be fitted closely by the sigmoid equation:

$$R = -0.24(x-675)^{1/5} + 33$$

This equation describes accurately the behavior of the subjects whose water intake was limited, but whose osmotic excretions varied from very low to very high. Above a critical osmotic excretion of 675 milliosmols per day, the test dose of water was retained by dehydrated subjects; below that critical value, the test dose of water was excreted even though the subjects were dehydrated. The dividing line, as indicated by the exponent 1/5, was very sharp.

Our results suggest that the water tolerance test can be used to assess state of hydration only under certain specific conditions. Distinction can be made between the normally hydrated individual and the dehydrated subject whose previous osmotic intake has been moderate to high. In the former, the test dose is excreted; in the latter, it is retained. However, in the dehydrated subject who is also osmotically depleted, the test dose is excreted just as in the normally hydrated subject, and no clear distinction can be made between these individuals by the water tolerance test.

Water tolerance tests are in current use for studying renal and adrenocortical function. The physiologic explanation offered above for results of loading tests in experimental dehydration with or without osmotic depletion suggests that clinical interpretation of such tests should include a consideration of the possible effects of the previous history of the patient with respect to water and osmotic balances independently of, or associated with, his disease.

Although our studies have been on healthy young men, the data summarized in Figure 2 might have some clinical implications related to the therapeutic use of diets of small osmotic effect. Diets of very low osmotic effect, such as pure carbohydrate, under conditions of enforced water deprivation do not conserve total body water as effectively as diets of intermediate osmotic effect. Furthermore, even with unlimited water, the subject on a diet of very small osmotic effect tends to lose total body water, and almost certainly part of this phenomenon may be attributed to voluntary dehydration induced by diminution of thirst.

THE CONCENTRATING ABILITY OF THE KIDNEY

Historically, the ability of the kidney to produce concentrated and dilute urine has been the most important single test of renal function. There has been an increasing tendency to re-

TABLE VII

Characteristics of nutrient combinations (Four to seven subjects subsisted on each regimen for two weeks)

Code*	Dietary intake			Urinary osmotic excretion	
	Calories *Cal/day*	Nitrogen *gm N/day*	Sodium *mEq Na/day*	*mOsm/day*	*Rank*
STO	0	0	1	497	8
0/100/0	1000	0	6	343	9
0/100/0	2000	0	9	275	10
2/20/78	1000	1.3	78	557	7
2/20/78	2000	2.2	157	653	5
15/52/33	1000	5.6	62	581	6
15/52/33	2000	11.4	178	791	3
15/52/33	3000	16.6	213	1080	2
30/0/70	1000	12.0	55	762	4
30/0/70	2000	23.8	107	1213	1
Control	ca 3600	ca 16	ca 150	1200	---

*The identification of regimens is based on the percentage of calories provided from protein, carbohydrate, and fat, respectively. STO was starvation.

place the measurement of concentrating ability in terms of total solids (specific gravity) by measurement of that function in terms of excretion of osmotically active substances (freezing point depression). Qualitatively, it is well known that water excretion and the concentration of the excreted urine may be affected markedly by alteration in diet. In order really to interpret the meaning of urine volume and urine concentration it is necessary to have knowledge of the subject's water balance and of his osmotic balance. A quantitative expression of the interrelations among diet, urinary volume, and urinary concentrating ability is essential for a comprehensive understanding of these phenomena.

In our experiments, minute urinary volume was measured under the rigidly controlled conditions described above and the osmotic concentration of serum and urine calculated from the freezing point depression (Fiske Osmometer).

By "osmotic load" (L) we mean the *rate of urinary osmotic excretion.* The osmotic effect of any of our regimens (Table VII) depends upon exogenous factors, such as protein and electrolyte intake, and endogenous factors, especially ketone bodies in three of the regimens. starvation, high protein, and high fat diets. The lowest osmotic loads were imposed by regimens high in carbohydrate, intermediate loads by diets containing moderate amounts of protein or salt, and high loads by diets relatively rich in protein or salt.

The quantitative mathematical treatment of these data has resulted in a unified single equation. Three transformations yielded an equation whose interesting implications are

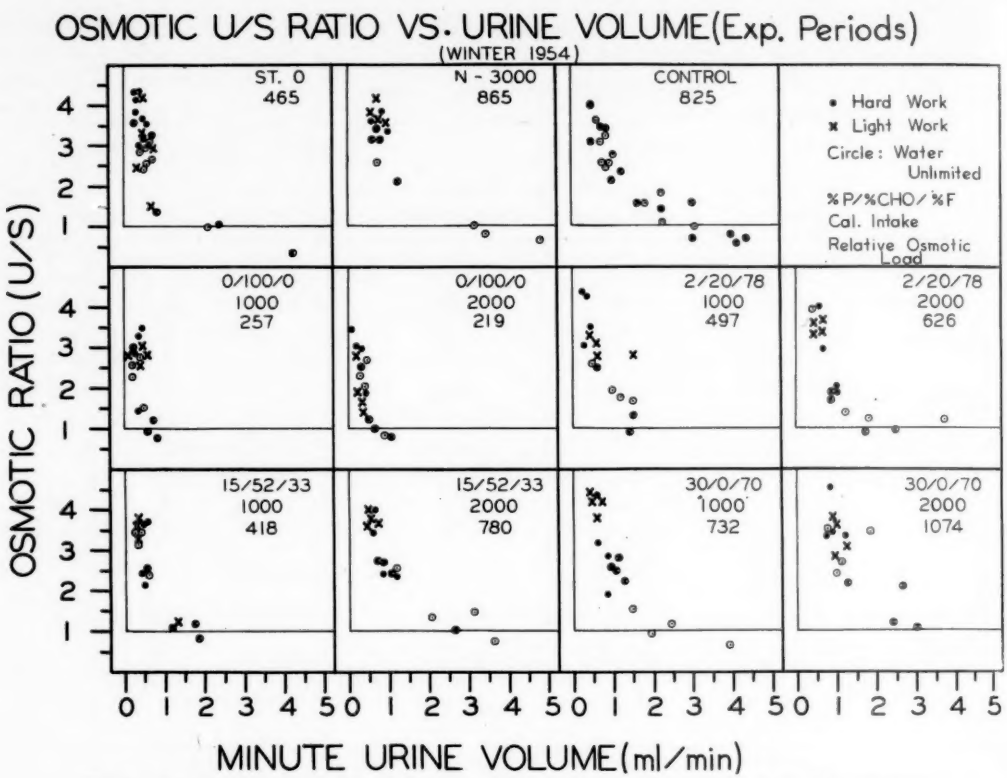

Fig. 3. Osmotic urine/serum (U/S) ratio vs. urinary volume for men on fixed nutrient regimens.

presented as the subject of this section.

Transformation 1: For each regimen V_1 and V_0 were determined by inspection. A conventional treatment[19] has represented the relation between the urine/serum osmotic ratio and minute urinary volume by means of an exponential curve of which the two asymptotes are: the obligatory volume, V_0, and the isosmotic volume, V_1. Figure 3 represents a portion of our data plotted in this manner. The obligatory volume, V_0, is commonly defined as the least minute urinary volume that is observed when the kidney is concentrating maximally. We have defined the isosmotic volume, V_1, as that urinary volume for subjects on a fixed regimen when the osmotic urine/serum ratio becomes 1.0. Unless the subject is on a fixed regimen, the values for V_0 and V_1 are so variable as to be of little use in calculations such as we are describing.[25]

Transformation 2: V_1 and V_0 were separately plotted against the osmotic load, yielding regression lines of very high correlation when fitted by the method of least squares. Figure 4 presents all of our data summarized for temperate, cold, and hot conditions. Each point in Figure 4 was derived by inspection from an exponential plot for each regimen, as illustrated in Figure 3. The remarkable uniformity of these data is striking.

Transformation 3: Regression equations for V_1 and V_0 (Fig. 4) were divided one by the other. Reassembling the components yielded the relationship:

$$\frac{V_1}{V_0} = \frac{5.22\ (L - 47.70)}{(L + 17.96)}$$

Implications

There are several interesting implications of this general equation. First, the maximum possible concentrating capacity of the kidney

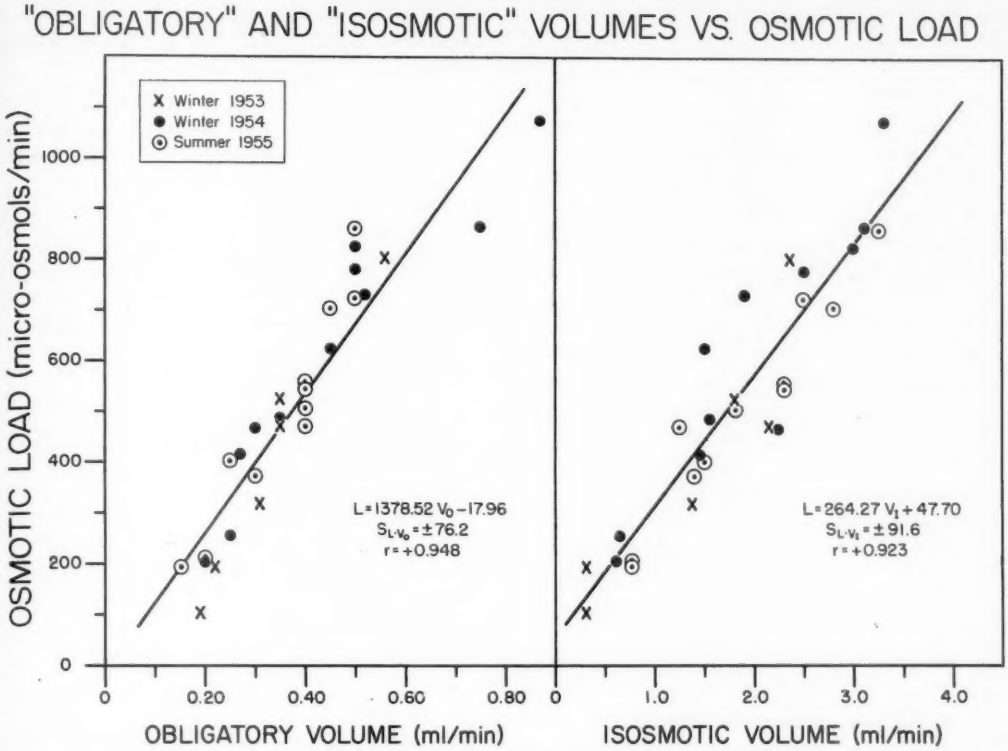

Fig. 4. Interrelationship between osmotic load and obligatory urinary volume and isosmotic urinary volume. All subjects on fixed nutrient regimens.

can be calculated when L becomes very large. Under those conditions, the numerator and denominator approach equality and the equation simplifies to $V_1/V_0 = 5.22$. This number must represent that maximum. Second, as L decreases the concentrating capacity of the kidney also decreases and for diets of very low osmotic effect, such as pure carbohydrate, may become as low as 3.0. Third, the general expression of the equation is that osmotic load must be considered one of the important parameters in any study of osmotic and water regulation and clearance by the human kidney.

Application

A possible application of the equation might be in establishing a simple quantitative test of renal function. If a patient were placed on a fixed dietary regimen of known osmotic effect and abundant fluids for a period sufficiently long to establish osmotic equilibrium, and then acutely deprived of water, the minute urinary volume would decrease progressively. Measurement of osmolarity of serum and urine periodically during this acute deprivation would result in a curve similar to those shown in Figure 3. From this V_0 and V_1 could be calculated and L is known.

The general equation can be recast in this form:

$$\text{Concentration Index} = \frac{V_1(L + 18)}{V_0(L - 48)}$$

In the normal subject, for each L there is an established concentration index from our data. We might expect that this concentration index for the damaged kidney would be abnormally low and perhaps might fluctuate with the pathologic state of the kidney. Possibly such an approach would have the advantage of quantitatively expressing the total kidney function as it relates to filtration and

reabsorption of water and osmotically active substances.

SUMMARY

Observations on renal function have been collected in 8698 subject-days in 211 healthy young men. Strict control of diet, fluid intake, and daily activity were maintained continuously. Temperate, cold, and hot environmental conditions were included. Three categories of observations of renal function were made: (1) standard qualitative and morphologic procedures, (2) standard quantitative tests, and (3) nonstandard studies of water and osmotic regulation. Many alterations can be provoked in renal function by nutritional imbalance, caloric deficit, dehydration, physical work, and extremes of temperature.

Glycosuria is extremely rare. Ketonuria is easily produced by nutritional imbalance, exposure to cold, or hard work. Transient albuminuria may be produced by an unbalanced diet or vigorous exercise, and exposure to cold accentuates this phenomenon. Microscopic hematuria and cylindruria may be produced by unbalanced diets, especially pure carbohydrate or starvation. When a predisposition exists, moderate exercise may accentuate the microscopic hematuria and cylindruria.

A combination of chronic dehydration and a diet containing over 12 grams of nitrogen per day increases the concentrations of urea, creatinine, and nonprotein nitrogen in the serum. Caloric deficiency decreases creatinine and urea clearances. Gross variations in diet can produce large alterations in the clearance values for sodium, chloride, and total osmolar active substances.

In these investigations the experiments involved all possible combinations of water deprivation, salt deprivation, and protein deprivation, thus producing the three commonly recognized varieties of hydropenia; i.e., pure water depletion hydropenia, pure salt depletion hydropenia, and mixed salt and water hydropenia. In the chronically and severely dehydrated subject an ingested water load is retained only when the osmolar excretion exceeds 700 milliosmols/day. Therefore, without knowledge of the rate of osmolar excretion, one cannot conclude that a subject is well-hydrated merely because he excretes a copious volume of dilute urine after a water load.

Our data from healthy young men have been generalized into a single equation in which the parameters, osmotic load, obligatory urine volume, and isosmotic urine volume, are interrelated. The maximum possible concentrating capacity of the kidney is reached at a urine/serum osmolar ratio of 5.22. Osmotic load is an important consideration in any study of osmotic and water regulation and clearance.

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Nutritional Aspects of Acute Glomerulonephritis

By HYMAN J. ZIMMERMAN, M.D.*

ADDIS[1] has stated that there is "complete anarchy" in the modern teaching of the role of diet in the treatment of glomerulonephritis. Rudebeck[2] has also emphasized the contradictory and diverse opinions which have been expressed regarding appropriate therapy of this disease. Many authors[3–10] today may recommend a dietary regimen differing little from that outlined 40 years ago.[11] Thus, both contradiction and lack of change have resulted from an inadequate experimental foundation for the clinical management of acute glomerulonephritis. A theoretical basis for treatment has been proposed by Addis,[1] who has reported extensive supporting experimental observations. Fahr and Smadel[12] have studied the effect of the amount of dietary protein on the course of experimental glomerulonephritis. There have been a few attempts[13–16] to evaluate the importance of dietary protein in the treatment of nephritis by controlled studies in humans. Other opinions on optimal treatment have been based only on theoretical considerations or uncontrolled observations of patients with the disease.[16]

PATHOGENESIS AND PROGNOSIS

Acute hemorrhagic glomerulonephritis is generally considered to result from an antigen-antibody reaction precipitated by infection with the beta-hemolytic streptococcus,[4] of which Type 12 has been particularly implicated.[17] The acute disease involves both kidneys diffusely with apparently complete recovery resulting in most cases.[4] Indeed, healing is reported[18–20] to occur in 95 per cent or more of children who recover from the acute state of the disease. In adults, however, chronic nephritis seems to result more frequently, with only from 60 per cent[18,21] to 80 per cent[2] recovery reported. Death occurs in the acute phase in 2 to 5 per cent of the cases.[1,21] Convalescence in some patients may be extremely prolonged. Addis[1] has stated that, even if the urinary sediment remains abnormal for two years or more after the attack, complete recovery may still occur.

GENERAL TREATMENT

There is little disagreement on the nondietary aspects of treatment. If there is still evidence of streptococcal infection of the pharynx, middle ear, skin, or elsewhere, appropriate antibiotics should be prescribed.[3,5] It has also been suggested[8] that even where there is no residual evidence of infection, penicillin therapy is indicated. The importance of bed rest until hematuria has subsided and the sedimentation rate has become normal is generally accepted.[3] Heart failure may be treated with digitalis and sodium restriction,[10] and hypertensive encephalopathy with parenteral magnesium sulfate.[16] It has also been shown that during the early phases of glomerulonephritis, renal blood flow may be improved by the use of this agent.[23] There is little evidence of benefit from nitrogen mustard or corticotropin (ACTH) in acute glomerulonephritis.

DIETARY MANAGEMENT

Concern with diet has keynoted most discussions of the treatment of this disease.[3] Implicit in diet therapy has been the aim to minimize the requirements for excretory function by the kidney.[1,3] Early diets consisting only of large quantities of milk were recom-

From Medical Veterans Administration Hospital West Side, Chicago and the Department of Medicine, University of Illinois College of Medicine.

* Chief, Medical Service, Veterans Administration Hospital and Clinical Associate Professor of Medicine, University of Illinois College of Medicine.

mended at a time when the azotemia of acute nephritis was considered to be the result of renal tubular obstruction by casts and debris. This regimen, however, usually failed to increase the urine volume and often led to increased edema. It has also been criticized as providing excessive amounts of protein.[3] At the other extreme is the regimen recommended by Volhard,[24] who advocated almost complete prohibition of food or liquid for the first few days of the disease. Diets rich in carbohydrate and fat, but poor in protein, salt, and water were also among the early diets recommended.[3] More recently "the importance of a qualitatively and quantitatively adequate diet especially in protracted cases" has been emphasized.[2]

Renal Work

Reasoning by analogy with the principles of the treatment of other tissue injury, Addis[1] has re-emphasized the importance of rest for the kidney injured by glomerulonephritis. He reasoned that the important work of the kidney is the resorption of water from the tubule against the resisting force of the increasing osmotic pressure exerted by the contents of the tubular lumen. The higher the degree of concentration of any single urine constituent during the process of urine formation, the more effectively does it increase the osmotic pressure of the tubular lumen contents. Since urea is concentrated over 60 times during the conversion of the plasma ultrafiltrate to urine, and since the daily amounts excreted are large, Addis[1] was able to calculate that over three-fourths of the theoretical osmotic work performed by the kidney was related to the excretion of urea.* Since urea excretion increases with increased protein intake, he suggested that the work of the kidney could be directly related to the amount of protein ingested.

Leiter[27] has advanced an additional theoretical basis for the restriction of dietary protein, namely the effect on antibody production. When the protein content of the diet is quantitatively or qualitatively deficient, antibody production is impaired.[28] He has suggested, accordingly, that a possible virtue of protein restriction in acute glomerulonephritis may be a decrease in the production of the antibodies considered responsible in the pathogenesis of the disease. There are no clinical data to support this possibility, but relevant experimental observations have been reported by More and Waugh.[29] These workers found that "mild starvation" seemed to protect against the development of experimental glomerulonephritis. The applicability of this concept to human glomerulonephritis, once developed, remains to be established.

Addis[2] has supported his contention by a series of experiments showing that the size of the rat kidney increases as the protein intake is increased. Studies by him as well as by Camara, Reimer, and Newburgh[25] have shown that the osmotic work of the kidney in humans with normal or diseased kidneys also increases with increase in the protein content of the diet. Addis,[1] furthermore, showed that animals with 75 per cent of their renal tissue removed had a progressive decrease in urine urea and an increase in blood urea with increasing protein in the diet. These studies corroborate the effect of dietary protein on renal osmotic work, but they do not prove that the completeness of recovery from nephritis is enhanced by protein restriction during the acute phase, or that chronic nephritis is more likely to develop in patients taking a normal or high protein diet. More closely related to the problem is the work of Fahr and Smadel.[12] These investigators found that rats with Masugi nephritis, considered by some to be an analogue of human glomerulonephritis, improved or recovered when maintained on a low protein diet. Those fed a high protein diet, however, worsened and died. Similarly, Addis[1] showed that the survival rate of rats with three-quarters of their kidney tissue removed increased progressively with decrease in dietary protein. McCann[30] has objected, however, to the applicability of the data obtained from nutritional studies in

* Addis[1] and Camara, Reimer, and Newburgh[25] used the following formula of Von Rohrer[26] or a modification of it. Work = NRT (2.3 loq. U/B − (U − B/U) in which N = Mols of excreted substance; R = the gas content; T = absolute body temperature; U = concentration of the substance in the urine, and B = concentration of the substance in the plasma.

experimental glomerulonephritis to the treatment of humans with nephritis.

Clinical Studies

Indeed, Schwenson,[13] in a study of a small group of patients, with "unsatisfactory"[16] controls, reported earlier recovery in patients receiving a high protein diet than in those whose dietary protein was restricted. Naeraa[14] and Mortensen[15] were unable to demonstrate any clinical advantage in patients receiving a low protein diet. Illingsworth, Philpott, and Rendle-Short[16] in a controlled study could demonstrate no significant differences in the speed of recovery between a group of children receiving a diet low in protein (0.25 g per lb) and a control group partaking of liberal amounts of protein (1.23 g per lb). The marked difference between the prognosis of acute nephritis in adults and children,[18] however, makes the application of the results of this study difficult to apply to adults. Addis[1] has stated, too, that his "clinical experience of many years" has "seemed to confirm" the theory of the importance of protein restriction.

Despite these controversial data on the validity of restriction of protein in the treatment of acute nephritis, there are important areas of agreement in the regimens suggested by Addis,[1] Fishberg,[3] Earle,[4] Pratt,[5] Merrill,[6] Lindberg,[7] and Schreiner.[8] These workers recommend marked protein restriction at the onset of the disease. Others[2,9,10] emphasize the importance of protein restriction only when there is azotemia, and state that in the milder episodes of acute nephritis such restriction is not necessary. The amount of protein recommended by Addis[1] for the acute phase of the disease is 0.2 g per kilogram body weight.

Diet in Convalescent Phase

The rate of increase of dietary protein during convalescence has depended on several criteria. Derow[9] has indicated that "a more liberal diet" may be instituted after edema, oliguria, and hypertension have subsided. Fishberg[3] has stated that "after a few days" more protein may be allowed, while Addis[1] has emphasized the importance of the urinary sediment in indicating sufficient improvement to allow an increase in the protein intake. A significant decrease in the rate of epithelial cell excretion has been interpreted[1] as sufficient evidence of improvement to allow successive but small increases in the amount of protein up to 0.5 g per kilogram of body weight for the adult and 0.75 g per kilogram for the child. In the regimen of Addis[1] larger amounts are not given at any time until complete healing has apparently occurred. When in subsiding nephritis or thereafter, there is marked proteinuria, with or without the fully-developed nephrotic syndrome, he has recommended that the protein ration shown above be supplemented by an amount equal to the daily urinary loss of protein. It is with this prolonged protein restriction that most workers do not agree. Fishberg,[3] Derow,[9] Rudebeck,[2] and others[4,5] have recommended that there be no limitations of dietary protein beyond the acute phase of the disease. Indeed, a high protein diet has been recommended for patients with marked proteinuria since the pioneer observations on the nephrotic syndrome by Epstein.[31] But further discussion of the treatment of this stage of glomerulonephritis is not within the scope of this communication.

It has recently been emphasized that restriction of dietary protein must be accompanied by an adequate calorie intake.[32] Kolff,[33] Borst,[32] and others[1] have shown that fasting is as deleterious in uremia as is protein feeding, since endogenous protein catabolism releases urea and potassium. These workers have utilized the protein-sparing effect of a diet high in carbohydrates and fat in the management of acute renal failure. This rationale also seems to apply to the treatment of acute glomerulonephritis.

There is general agreement that the intake of sodium chloride should be restricted when there is edema and hypertension.[1–11] Earle[4] has stated that dietary salt should be low even in the mildly ill patient. This restriction may be removed when the patient has returned to clinical normality.

It has been emphasized[4] also that the fluid intake should be sharply limited to no more than 700 ml daily in the oliguric or anuric patient. This approach may need modification

in the presence of vomiting and dehydration.

CONCLUSIONS

Restriction of dietary protein during the azotemic, oliguric phase of acute glomerulonephritis is generally accepted. It is difficult to establish clinically the validity of limitation of protein restriction in the absence of uremia or during convalescence. Nevertheless, the author believes that the protein intake recommended for the mildly ill or convalescent patient should follow the regimen of Addis, since the theoretical basis for such dietary restriction seems reasonable, and is supported by the animal studies. There is no evidence of an adverse effect of this regimen and the amounts of protein allowed are sufficient to maintain nitrogen balance. Restriction of sodium chloride should be practiced at least during the edematous hypertensive phase of the disease and perhaps beyond.

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Dietary Treatment in Acute Anuria

By K. G. LOWE* AND H. VALTIN†

ANURIA is a dramatic emergency requiring prompt clinical assessment and institution of rational therapy. Therefore, before beginning dietary management, it is necessary to determine the type of anuria, and whether there is need for urological procedures and therapeutic measures other than diet.

TYPES OF ANURIA

Anuria may be due to obstruction of the urinary pathways (obstructive or post-renal anuria), to temporary depression of renal blood flow due to disturbances of the general circulation (acute circulatory renal failure or pre-renal anuria), or to any of the known causes of kidney disease (renal anuria).

Post-renal Anuria

"Surgical anuria" is sometimes used as a synonym for post-renal anuria since diuresis can be frequently and promptly obtained by urethral or ureteral catheterization. Failure to recognize and relieve obstructive anuria is tragic but fortunately rare. We have encountered only one such case, that of a 71-year-old woman in whom a large uterine fibroid had become impacted in the pelvis, obstructing both ureters and the lower end of the ileum and causing vomiting, colicky abdominal pain, and anuria. Laparotomy with removal of the fibroid would have relieved both ureteral and small intestinal obstruction, but surgery was denied her as she was thought to be "too poor a surgical risk" (Fig. 1).

There are, however, some types of obstructive anuria in which it is legitimate to treat the patient conservatively and await spontaneous diuresis. We have described elsewhere a patient with tuberculosis of his single remaining kidney (the other kidney having been removed surgically eight years previously) who developed ureteral obstruction due to caseous material and was treated conservatively i.e., with a single, initial urethral catheterization, but without cystoscopy or ureteral catheterization. After five days of anuria he spontaneously passed some caseous material and thick pus, and thereafter had a profuse diuresis with fall of blood urea nitrogen from 100 mg per 100 ml to normal levels.[1] Similarly, the majority of patients with sulfonamide obstructive anuria achieve spontaneous diuresis within a week and need no urological treatment.[2] No harm is done to the remaining cases by postponing ureteral catheterization for a week, as there still remains a "grace period" of at least another week before irreversible renal damage could occur.[3] It is important to limit the number of such catheterizations, as they may cause serious infection. We have seen fatal peritonitis following rupture of an inflamed bladder by a cystoscope, in a patient with sulfonamide obstructive anuria who had had several unnecessary urethral catheterizations. We have also seen fatal pyelonephritis in a patient with acute tubular necrosis following a single, needless ureteral catheterization. Finally, urinary tract infections, as well as infection elsewhere, hasten the development of biochemical derangements in anuria.

In summary, then, while many cases of obstructive anuria can and should be relieved by immediate urethral or ureteral catheterization, in a proportion expectant treatment may be preferable.

Pre-renal Anuria

In this condition, also known as acute circulatory renal failure, there is severe but short-lived (usually only a matter of hours) depression of renal blood flow and glomerular filtra-

* Lecturer in Medicine, University of St. Andrews, Scotland.

† Holder of Traineeship from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

tion rate secondary to disturbance of the general circulation. It is seen particularly in states of shock (cardiogenic, neurogenic, anaphylactic, or oligemic) and dehydration (depletion of water, sodium, or both). Figure 2 shows diagrammatically how in oligemic shock, with reduced cardiac output, there is a redistribution of blood flow to the various vascular beds of the body, with especially marked reduction in renal blood flow. When the general circulatory disturbance is corrected, for example by restoration of blood volume and peripheral blood pressure, urine flow returns promptly. During the period of renal ischemia there may be some damage to the tubular epithelium, but within critical limits of duration and severity of renal ischemia, this damage is insufficient to prevent diuresis. Beyond this critical limit of renal ischemia, there ensues widespread necrosis of tubular epithelium and tubular cast formation (acute tubular necrosis, discussed in the next section) with anuria persisting after the correction of the general circulatory disturbance. Figure 3 illustrates an episode of oligemic shock with brief anuria. Rapid replacement of blood loss in this patient prevented a severe lesion (acute tubular necrosis) with prolonged anuria.

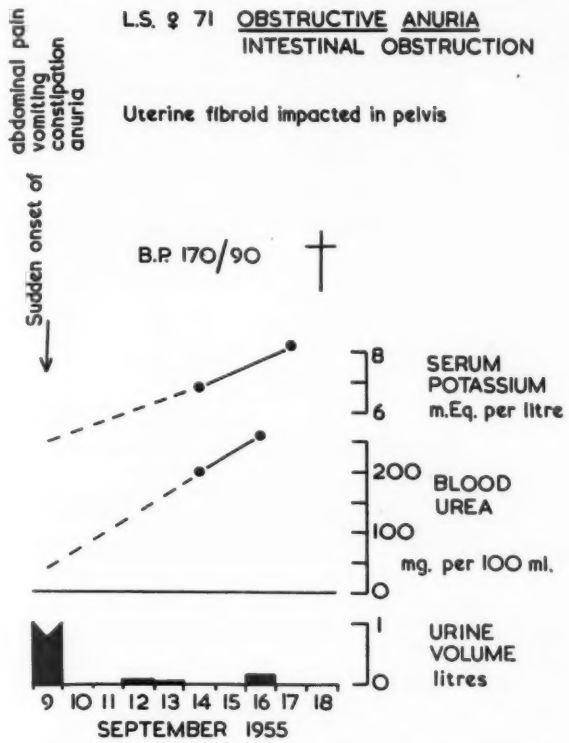

Fig. 1. Course of illness in patient with impaction of fibroid in pelvis which led to death from the effects of obstructive anuria and intestinal obstruction.

Renal Anuria

Anuria may occur terminally in any chronic renal disease, and several acute diseases such as leptospirosis, renal medullary necrosis, and severe glomerulonephritis may lead, though relatively rarely, to anuria. But by far the most common acute renal lesion manifesting anuria is acute tubular necrosis, also known by various other terms, such as lower nephron nephrosis or acute tubulo-interstitial nephritis. Common causes of acute tubular necrosis are acute poisonings (e.g., carbon tetrachloride,

mercury, phenol, oxalic acid), intravascular hemolysis (e.g., mismatched blood transfusion, "Blackwater Fever"), induced abortion, premature separation of the placenta, and severe trauma (e.g., battle and air-raid casualties, industrial and traffic accidents). In the most severe examples of these mishaps there may be glomerular as well as tubular damage in the form of focal or complete renal cortical necrosis. In fact, depending on the severity of the noxae, there may be seen, in any large series of cases, graded severity of renal failure, from short-lived episodes of anuria due to a mild renal tubular lesion up to inevitably fatal anuria due to complete cortical necrosis. This graded severity has been demonstrated most clearly in premature separation of the placenta.[4,5]

Renal damage can be kept to a minimum by suitable treatment or prophylactic measures during the onset phase of acute tubular necrosis. The prompt treatment of oligemic shock by blood transfusion and the early administration of BAL in mercury poisoning are obvious examples. Renal sympathetic block in cases of premature separation of the placenta has been advocated by some authors, but its efficacy is not yet proved.[6] The practice of maintaining a water or an osmotic diuresis during blood transfusion might minimize renal damage in hemolytic transfusion reactions. Pressure dressings applied to the affected area in cases of "crush syndrome" may help to lessen tubular damage.[7] When extensive necrosis of the tubular epithelium has occurred, however, prolonged anuria or oliguria (less than 300 ml of dilute urine per day in an adult) inevitably follows.

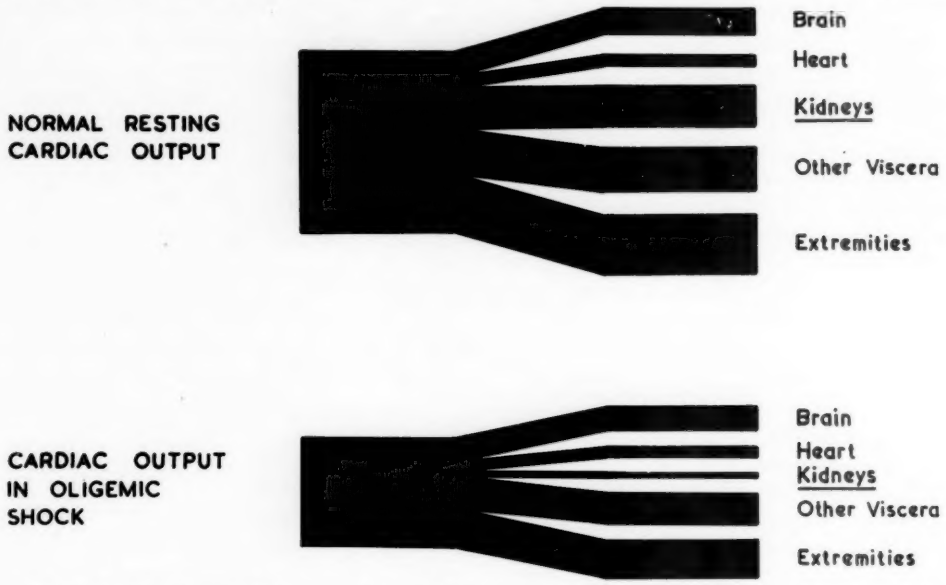

Fig. 2. In disturbances of the general circulation there are readjustments of the blood flow through the various vascular beds of the body. In many patients with shock there appears to be especially marked reduction of renal blood flow.

THE MAJOR BIOCHEMICAL DERANGEMENTS IN ANURIA

The biochemical derangements in anuria vary widely in severity and pattern. The majority of cases, however, due to whatever cause, follow the pattern illustrated in Figure 4. There is an initial rapid rise in the blood urea level which tends to level off after a few days. The rise is particularly steep when there is excessive catabolism due to infection, tissue necrosis, or continued intravascular hemolysis. The serum potassium rises unless the release of intracellular potassium into the extracellular fluid is offset by potassium loss due to

diarrhea, vomiting, or drainage from intestinal fistulae. It may rise quickly to a lethal level, the patient dying suddenly (and unexpectedly if serial electrocardiograms or biochemical studies have not been done). Water or sodium imbalance may occur, singly or together, due chiefly to failure in management. Both water and sodium may be given in excess, resulting in expansion of blood volume and extracellular space, with consequent systemic arterial and venous hypertension, generalized edema, and, most serious of all, pulmonary edema. On the other hand, if too much water is given in excess of sodium, there may ensue water intoxication manifested by convulsions or coma or both. Finally, metabolic acidosis usually develops, although in rare cases alkalosis may be brought about by excessive administration of alkalis, such as intravenous sodium lactate. Sometimes it is difficult to say which of several associated biochemical features of uremia may be responsible for death. But as Bull has emphasized,[8] there are many clinical pictures of uremia, the symptoms—and certainly those that endanger life—being due more to water and electrolyte imbalance than to the accumulation of organic end-products of nitrogen metabolism.

In surviving patients, recovery of renal function is associated with a diuretic phase, in which the chief dangers arise from rapid depletion of water and electrolytes. At the onset of diuresis, urinary losses of water and salt are poorly controlled for two reasons. One is the osmotic diuretic effect of the high blood urea level. The other is reduced function of the immature, regenerating tubular epithelium in cases of acute tubular necrosis. Thus, great care must be exercised during this phase to replace water and electrolytes adequately.

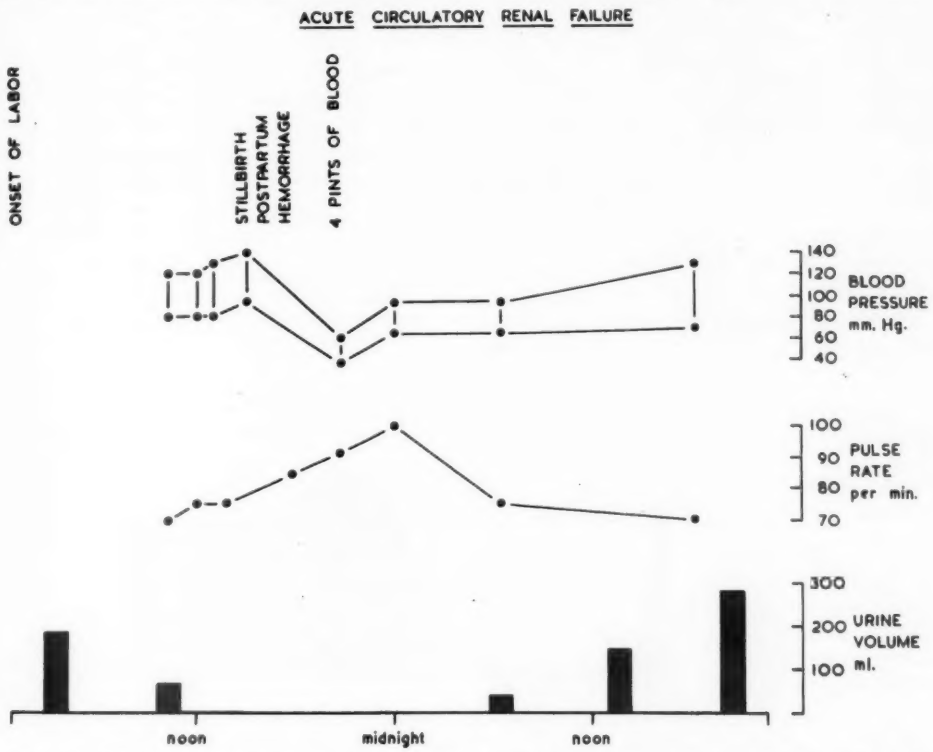

Fig. 3. This figure illustrates an episode of shock due to severe postpartum hemorrhage. During the shock episode there was virtually no urine flow, but in association with the restoration of blood pressure there was prompt return of urine excretion.

Sodium depletion with fall in blood pressure may lead to a second episode of decreased urine flow; potassium depletion may result in stupor, paralysis, or cardiac irregularities; and loss of water in excess of sodium can lead to hypernatremia and cerebral damage.

the beginning of the anuric or oliguric phase, assuming, of course, that treatment for the basic cause of the renal lesion, such as specific antidotes for poisons or corrective measures for oligemic shock, etc., have already been instituted.

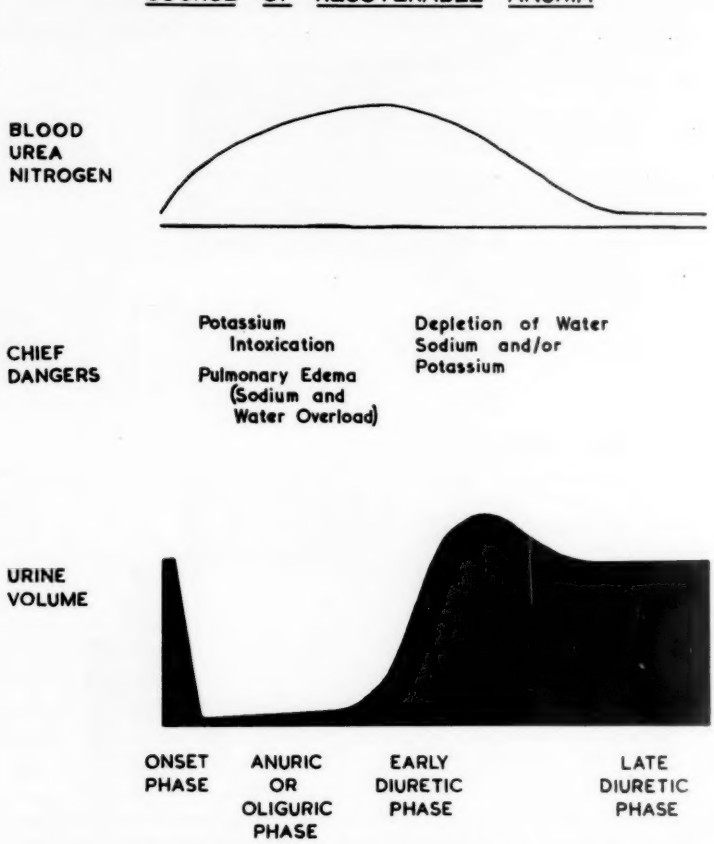

Fig. 4. This figure illustrates the most common pattern of anuric episodes. The "hump" in urine volume during the early diuretic phase is seen frequently but not invariably.

Throughout the course of the anuric and diuretic phases there are other dangers, such as the well-known predisposition of anuric patients to infections and to poor wound healing. Thus, in patients who have undergone recent laparotomy, wound dehiscence is unduly frequent.

THE TREATMENT OF ANURIA

We shall open the discussion of treatment at

Dietary Management

The dietary management of anuria has three important aims: (1) to keep the accumulation of nitrogenous end-products to a minimum; (2) to prevent hyperkalemia; and (3) to prevent overloading with water or sodium, or both. The first two of these aims are accomplished by a diet designed to reduce protein catabolism to a minimum. The third aim is

accomplished by careful regulation of the water and sodium intake.

Reduction of Protein Catabolism: Catabolism, and with it the accumulation of nitrogenous end-products, is kept to a minimum by a protein-sparing diet, i.e., one which supplies a large number of calories from carbohydrate and fat. This fact has been demonstrated repeatedly over the past fifty years, and has been re-emphasized by Borst.[9] While the original aim of the protein-sparing diet was to prevent the accumulation of nitrogenous end-products, it now appears that the most important feature of such a diet is that, in minimizing tissue breakdown for energy requirements, it slows down the release of intracellular potassium into the extracellular fluid.[8] The effectiveness of an electrolyte-free, protein-free, high calorie diet in reducing urea formation and cellular release of potassium to a minimum has been shown in normal subjects. For example, in adult males fed 1 liter of water, 300 g of glucose, and 150 g of peanut oil daily (total intake of 2550 calories), the average daily urinary excretion fell within a few days to less than 3 g of urea nitrogen and about 10 meq each of sodium, potassium, and chloride, the blood urea nitrogen level falling and the plasma electrolyte levels being maintained.[10]

The daily allowance of carbohydrate and calories varies according to different authors, and is outlined below. Although some give only 100 g of carbohydrate a day,[11,12] others recommend much larger amounts, sometimes with added fat.[9,13,14,15] Carbohydrate may be given in the form of sucrose, glucose, lactose, or starch. The inclusion of fat, such as peanut oil, as a supplement to carbohydrate is optional and is now used much less frequently than formerly.

The protein-sparing diet must be continued throughout the anuric or oliguric phase, but during the diuretic phase, as the blood urea nitrogen and potassium levels fall, some relaxation may be allowed, and a more palatable, oral, low protein diet may replace such severe regimens as intravenous infusion or tube feeding of glucose solutions. Once the serum potassium level begins to fall there is the new danger of hypokalemia (Fig. 4), and potassium supplements must be provided in the diet to replace further losses in the urine.

Water and Sodium Balance: There is no doubt that in the past the two commonest avoidable causes of death in anuria were pulmonary edema due to overloading with salt and water, and potassium intoxication. The latter has been discussed in the preceding section. The amount of fluid replacement should equal the losses in urine and by extra-renal means (water of respiration, perspiration, and gastrointestinal losses such as vomiting, diarrhea, and drainage from fistulae) *minus* the water of oxidation from ingested carbohydrate and fat, and water released from cellular breakdown. It has now been shown conclusively that fluid replacement which equals the total extra-renal loss without allowance for water of oxidation will lead to cellular overhydration.[16] In actual practice, in the absence of marked gastrointestinal loss or sweating, the daily fluid intake for an anuric adult should be about 500 to 700 ml. The daily fluid intake in anuric infants varies with age and size, and has been outlined by Talbot and his co-workers.[17]

The daily determination of serum electrolytes (sodium, potassium, bicarbonate, and chloride) is helpful, but it has been our experience that, with the exception of hyperkalemia, few patients require correction of serum electrolyte abnormalities during the anuric phase. In fact, while mild metabolic acidosis is common, that probably is less harmful to the patient than overzealous treatment with sodium salts. Richet *et al.*,[18] on the other hand, have shown in dogs and rats that protein catabolism is maximal when the body fluids are hypotonic. For that reason, as well as in cases of *symptomatic* acidosis, a particularly low serum sodium, as might be caused by excessive sodium losses in the urine, sweat, or from the gastrointestinal tract, calls for correction. Sodium bicarbonate or lactate should be given to acidotic patients, while sodium chloride should be used in cases of alkalosis.

With the onset of the diuretic phase, the pendulum suddenly swings in the opposite direction, and more serious errors can result from under- rather than over-treatment

(Fig. 4). During this phase, sodium and water must be replaced vigorously. Total daily fluid replacement should equal all measured fluid loss (urine plus gastrointestinal losses if present) plus an allowance of 500 to 700 ml for insensible water loss. Sodium losses must be measured and replaced daily, in a similar fashion, to prevent sodium depletion or water intoxication or both. In the absence of urinary sodium estimations or of large extra-renal losses of sodium, it is a good rule of thumb to give 1 liter of normal saline (or other isotonic sodium solution) and 1 liter of dextrose in water for every 2 liters of urine passed. This rule is based on the observation that during the early diuretic phase the urine sodium concentration is approximately half the serum sodium concentration. This careful replacement of water and sodium must be continued until the blood urea nitrogen level has returned to normal.

Fig. 5. This patient had an incompatible blood transfusion, severe oliguria for 8 days, and a maximal blood urea nitrogen of 170 mg per 100 ml. She was tube-fed a fat-sugar emulsion throughout the course of illness and kept in good salt and water balance.

Routes of Administration: The diets which are outlined below may be administered by three routes. Usually the choice of administration is determined by the severity of the illness. Oral diet is adequate for many patients, especially those in whom early diuresis is expected, whose general condition is good, and who are not vomiting. Common causes of these milder anurias include mild hemolytic

transfusion reactions, brief episodes of oligemic shock, and mild cases of premature separation of the placenta without toxemia of pregnancy. Kolff has used the term "forced" high calorie diet, emphasizing the fact that many patients need constant persuasion to ingest amounts of carbohydrate sufficient to prevent protein catabolism for energy requirements.[19] While these diets are not particularly palatable, and despite the anorexia which frequently accompanies anuria, many patients are able to cooperate adequately if the importance of the high calorie diet is explained to them.

For patients in whom diuresis is not expected until the second week or later, as in mercury poisoning, induced abortion, severe traumatic cases, or severe hemolytic transfusion reactions, intra-gastric or intra-duodenal tube feeding of glucose solution or fat-sugar emulsion may have to be resorted to. Polyethylene tubing, not exceeding 2 mm in its outside diameter, is usually well tolerated over long periods of time. The emulsion can be run in from a blood-bank delivery set via a cannula inserted into the polyethylene tubing (Fig. 5). The rate of flow should be only a few drops per minute.

In patients who, because of gastrointestinal lesions or for any other reason cannot tolerate oral diet or tube feeding, recourse is had to intravenous infusion. Hypertonic glucose solution (e.g., 40 per cent) best accomplishes the dual purpose of adequate caloric intake and fluid restriction. If this solution is given through a cardiac catheter or wide bore polyethylene tubing into the superior or inferior vena cava via limb veins, venous thrombosis and clotting within the catheter usually can be prevented. Heparin sodium, 15,000 units (150 mg)/day should be added to the solution.[20]

In actual practice it is often found best to use a combination of the above routes of administration, or to alternate them. No rigid rule can be prescribed, and the actual regimen must be suited to the individual patient.

Non-dietary Measures

Two non-dietary measures in particular must be mentioned here, as failure to observe them would counteract the dietary regimen and might endanger life. The first concerns the reduction of the serum potassium. Despite the strictest dietary regimen, the serum potassium may continue to rise. Daily estimations of the serum potassium will give warning of potassium intoxication, and as soon as the level reaches some arbitrary limit, such as 6 meq per liter, treatment with ion-exchange resin should begin. It is probably best to administer the sodium-charged sulfonic or carboxylic resin orally if tolerated, or else by retention enemas.[15,21] In these resins sodium will be exchanged for potassium in the bowel.

The second important non-dietary measure is the prevention of infection. We have seen earlier that the dietary regimen seeks to reduce protein catabolism to a minimum. Infection increases protein catabolism by raising the energy requirements of the body, and by tissue breakdown. All anuric patients, therefore, should receive prophylactic antibiotics. Penicillin is adequate in most cases, and can be given in smaller dosage than usual as there is no renal excretion of the drug. A daily injection of 1 million units of crystalline penicillin is adequate.

If the patient continues on a downhill course despite vigorous dietary measures, then the artificial kidney or other forms of dialysis may have to be resorted to.[15,22] A discussion of these measures, however, is beyond the scope of this paper.

OUTLINE OF TREATMENT OF ANURIA

I. Onset Phase

Correct factors responsible for pre-renal anuria, such as dehydration or oligemic shock.

If remediable obstructive anuria is suspected, consult a urologist. Avoid needless bladder catheterization, cystoscopy, and ureteral catheterization.

Give appropriate antidotes for nephrotoxin (e g., BAL for mercury poisoning).

In hemolytic transfusion reactions give immediately 1 liter of a 10 per cent glucose solution intravenously to maintain water diuresis in the hope of minimizing tubular cast formation and epithelial damage.

In cases of severe trauma apply pressure dressing to the affected part and replace blood loss promptly.

II. Anuric or Oliguric Phase

Isolate the patient to prevent infection, and give prophylactic antibiotics (e.g., 1 million units of crystalline penicillin daily).

Maintain the hemoglobin level above an arbitrary level (e.g., 10 g per 100 ml) by giving careful transfusion of packed red blood cells. The volume of the transfusion is not included in the daily fluid allowance.

Make daily determinations of the blood urea nitrogen, and of the serum sodium, potassium, bicarbonate, and chloride.

Take an electrocardiogram daily, preferably with precordial leads, to warn of hyperkalemia.

When the serum potassium level rises above 6 meq per liter, begin treatment with sodium-charged cation-exchange resin: (1) Sodium carboxylic resin, 20–60 g daily in divided doses, mixed with cold water, orally or by retention enemas.[15] Or—(2) Sodium sulfonic resin, 15 g three or four times daily, orally in water or syrup and/or by daily retention enemas, made up as follows:[21]

Sodium sulfonic resin	30 g
Emulsifying agent	As required
Distilled water	100 ml

Accurately measure and replace the total daily fluid output [Insensible loss (500 to 700 ml), plus any other extra-renal losses, plus any urine].

Diet

(a) Cases expected to have short and mild course of illness: Place the patient on a daily allowance of 200 g of glucose or lactose which can be dissolved in the daily ration of water and sipped at intervals throughout the day, or can be eaten in spoonfuls separate from the water. Lactose is less nauseating than glucose. This regimen can be tolerated for up to two weeks or more.[12]

(b) Cases expected to have long and severe course of illness: Choice of tube-feeding or intravenous regimens.

Tube Feeding (Intra-gastric or Intra-Duodenal): Pass a fine rubber or polyethylene tube into the stomach or duodenum. In an unconscious patient make certain that the tube has gone into the stomach by aspirating acid gastric contents or by injecting air while auscultating over the stomach for bubbling sounds. The following mixtures may be used:

According to Bull, Joekes, and Lowe:[13]

Glucose	300 g
Peanut Oil	150 g
Emulsifying agent (e.g., gum acacia)	As required
Vitamins	Optimal daily requirements
Water	to 1 liter

According to Brun:[14]

Glucose	100 g
Starch	100 g
Peanut Oil	100 g
Arabic Gum	50 g
Water	to 1 liter

According to Kolff:[15]

Glucose	200 g
Lipomul® oral or Ediol® *	200 g
Vitamins	Optimal daily requirements
Water	to 1 liter

To the emulsion can be added such supplements of water and salt as are required to balance losses from the gastrointestinal tract and, in oliguria, from the urine.

Intravenous Infusion into Vena Cava: If tube feeding is not tolerated or cannot be given because of ileus or other cause, then a cardiac catheter or polyethylene tube should be passed into the superior or inferior vena cava. The daily fluid requirement is given as 40 per cent glucose solution. By using a vena cava, venous thrombosis is rendered very unlikely, especially if 15,000 units (150 mg) of heparin sodium are added to the daily infusion. Barring obvious signs of venous obstruction or thrombophlebitis, the catheter may remain in situ for periods up to four weeks, by which time diuresis is to be expected in the vast majority of recoverable anurias.

Electrolyte Balance

In more severe cases, sodium loss should be estimated and replaced quantitatively. It can

* Lipomul® oral (Upjohn Co., Kalamazoo, Michigan). Ediol (Schenley Laboratories, Inc., 350 Fifth Avenue, New York, N. Y.).

be given as a mixture of sodium chloride and sodium lactate solutions, depending on the degree of acidosis present. Until biochemical analyses of the urine and alimentary losses are available, replace urine loss by equal parts of glucose and isotonic sodium chloride, gastric secretion by isotonic sodium chloride, and intestinal secretion by equal parts of isotonic sodium chloride and isotonic sodium lactate.

III. Early Diuretic Phase

Continue the above regimens until the blood urea nitrogen has fallen to about 50 mg per 100 ml and the serum potassium has returned to normal. Thereafter, palatable, low protein (30 g per day) diet can be given orally. Sample diets are given by Kolff.[15]

Particular attention must be given in this phase to adequate replacement of the sometimes excessive urinary losses of water, sodium, and potassium (Fig. 4). For this reason it is particularly desirable that all fluid voided be analyzed for sodium and potassium content. Potassium replacement is not required until the serum level has returned to normal.

SUMMARY

Immediate diagnosis and treatment are urgent matters in anuria. Extra-renal factors depressing renal blood flow should be corrected. Ureteral catheterization may be required for obstructive anuria, but judgment in the selection of cases is necessary.

Dietetic management should begin as soon as the diagnosis of anuria is established. Endogenous protein breakdown is kept to a minimum by high calorie, protein-free diet administered orally, by gastric tube, or intravenously. The patient is kept in meticulous water and sodium balance, and symptomatic acidosis and alkalosis are treated by an appropriate mixture of sodium salts when these are required to balance sodium output. Hyperkalemia is treated by giving sodium-charged cation exchange resin either orally or by retention enemas.

Even when spontaneous diuresis occurs, meticulous water and electrolyte balance and protein restriction must be continued until the blood urea nitrogen level approaches normal.

The patient is isolated and given antibiotics throughout the illness to prevent infection.

In some cases dialysis procedures are required in addition to the dietary regimen.

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Nutrition in Chronic Renal Failure

By ARTHUR J. MERRILL, M.D.*

THE MANAGEMENT of nutrition in chronic renal failure differs from that of acute renal failure in several respects: (1) The duration of the disease requires that the diet be adequate in caloric, vitamin, mineral, and protein content, and that it contain proper amounts of the essential amino acids. (2) It must be palatable, since tube feeding is impractical and undesirable for extended periods and because a tasty diet is essential to the morale of these patients whose appetite at best may be none too good. (3) Potassium intoxication is not as common as in acute renal failure, since the urine volume is usually ample except when the patient is moribund. (4) Fluid control is not as exacting as in acute renal failure, because the urine volume can adapt itself to the intake of fluids within variable limits.

PATHOLOGIC PHYSIOLOGY OF THE DIGESTIVE ORGANS IN CHRONIC RENAL FAILURE

A surprisingly small amount of information has been gathered about the function of the digestive organs in renal failure. The most striking change occurs in the digestive tract itself. This results to a considerable extent from the exposure of the damaged tissue to the action of the bacteria which are present in the intestines. The fibrinoid degeneration of the small blood vessels and the arteriolonecrosis produce ischemic and hemorrhagic lesions which furnish a fertile culture medium for bacterial proliferation. A further contributing factor is the formation of ammonia by urea-splitting enzymes and bacteria.[1] This leads to mucosal irritation. These disturbances, plus acidosis and retention of toxic products, produce anorexia and not infrequently nausea and vomiting which may defeat any effort to maintain nutritional balance. Stomatitis may be so painful that the patient will not take food or drink. Cerebral edema frequently causes nausea and vomiting. Esophageal irritation or ulcerations occasionally may cause dysphagia. Severe anemia or edema may lead to moderate digestive dysfunction.[2] Achlorhydria is said[3] to exist in chronic nephritis, not necessarily in chronic uremia, a statement which has several times been misquoted. Even this information cannot be accepted without reservation, since the author gives no substantiating figures and cites no references. He simply states that hypochloremia is rarely produced by vomiting in uremia, "probably because in most *chronic nephritics* a hypochlorhydria or achlorhydria exists." Actually, the total chloride remains high in the gastric juice of patients with chronic uremia, although there is little free acid present.[4] Potassium deficiency may be contributed to by the nausea and vomiting, as well as by the diarrhea. Salt depletion is favored by the same disturbances, and calcium deficiency is at least partly a result of the lack of responsiveness of the small intestine to the calcium-absorbing effect of vitamin D. This can be ameliorated by dihydrotachysterol, although other undesirable effects may be produced.[5]

Many bacteria are filtered through the liver and damage here might be anticipated. Little work has been reported concerning liver function in renal failure; liver function has been normal in most patients studied clinically by the author. This may be because the blood supply of the liver is so rich that ischemic lesions do not occur. Other digestive organs also seem to function very well.

THE FUNCTIONS OF THE KIDNEY

The general functions of the kidney are: (1) to eliminate from 40 to 60 per cent of all the water which is ingested or formed by the body;

34 Fourth Street, N. E., Atlanta, Georgia.

* Associate Professor of Clinical Medicine, Emory University Medical School, Atlanta, Georgia.

(2) to excrete waste products of protein catabolism such as urea, uric acid, creatinine and creatine, and sulfate; (3) to help preserve acid-base balance; (4) to help maintain a normal osmotic pressure in the blood and extracellular fluid, and through this, in other body compartments.[6]

By means of pressure in the glomerular capillaries, 180 liters of a cell-free, nearly protein-free, filtrate is filtered through the glomerular membrane each day. Roughly 85 per cent of the sodium chloride and water are reabsorbed by either the distal convoluted tubules or by the collecting ducts, the exact amount being determined by the influence of the antidiuretic hormone.[7] Thus about 0.5 to 1.0 per cent of the filtrate, or one to two liters daily, go into the formation of urine. An understanding of nutrition in renal failure is facilitated by a knowledge of several important actions by the kidney.

Sodium and chloride appear to be handled similarly by the proximal convoluted tubule which reabsorbs about 85 per cent of that filtered. Over this the adrenal cortex exerts a regulatory effect. In the distal convoluted tubule where acid-base balance is adjusted, H+ ions are excreted in the urine, permitting reabsorption of sodium ions. Also ammonia is formed chiefly from glutamine, and the ammonia combines with various anions permitting further conservation of sodium.[7]

About 2 per cent of filtered potassium is excreted. Much is reabsorbed by the proximal tubules and some is excreted by the distal convoluted tubules in acid-base adjustment. Excess loads of K+ are usually easily excreted by the normal kidney, provided the urine volume is adequate. Berliner believes that in the presence of potassium deficiency, additional H+ ions are excreted, since his work has indicated that H+ ions and K+ ions compete with each other for excretion.[8]

Only ionized calcium and a small amount of unionized calcium salts are filtered, the remainder being protein-bound. The amount of ionized calcium in the blood varies inversely with the blood pH and the inorganic phosphate excretion.[9] Acidosis increases the ionization and thus the filtration of calcium. The action of the parathyroid hormone may increase the filtration rate.[10] Parathyroid hormone is also involved in the intestinal absorption of calcium; it enhances the excretion of phosphorus by the kidney which promotes retention of calcium, since calcium and inorganic phosphate maintain a reciprocal relationship in the blood.

Phosphate reabsorption is almost complete at fasting levels, but after meals the tubular reabsorptive mechanism becomes saturated, i.e., the threshold is exceeded, and at a blood pH of 7.4 phosphate is excreted 20 per cent as H_2PO_4 and 80 per cent as HPO_4.[11] Vitamin D increases the intestinal absorption of calcium which suppresses parathyroid activity which, in turn, decreases urinary inorganic phosphate excretion, since the parathyroid hormone increases phosphate excretion by the kidney.[9] Phosphate excretion is greatly dependent on the glomerular filtration rate and is regularly retained when the filtration rate falls below 17 per cent of normal.

Sulfate ions are reabsorbed at low plasma concentrations, but any excess is rejected by the tubules and excreted in the urine in the dog.

About 57 per cent of urea is reabsorbed by the proximal and distal convoluted tubules.[7] A rise in blood urea indicates a loss of nephrons or else a reduction in glomerular filtration rate.

CHEMICAL ABNORMALITIES IN CHRONIC RENAL FAILURE

Acidosis is one of the most frequent chemical abnormalities in renal failure, partly because the end-products of protein catabolism are acid and the kidney is supposed to eliminate them, and partly because involvement of either end of the nephron results in acidosis.[12] On the one hand, a low glomerular filtration rate is associated with retention of acid phosphate, and, on the other, damage to the distal tubules causes loss of cations because of the inability of the injured tubules to make ammonia and excrete H+ ions in order to conserve base.

Alkalosis is rare in untreated patients for the reasons just mentioned.[14] As little as 2 to 4 g of sodium bicarbonate daily may result in alkalosis, whereas 1 to 3 g a day may permit acidosis to exist. This lack of elasticity of adjustment characterizes renal failure in almost

every modality.

The same inelasticity of adaptation applies to water balance. Vomiting, diarrhea, and the ineffectiveness of the antidiuretic hormone on the diseased distal nephron tend to produce water depletion. In the opposite direction, loss of nephrons or interference with filtration by thickening of the glomerular membrane cause water retention. J. P. Merrill[15] has pointed out that partial nephrectomy in animals[16] or loss of nephrons in human renal failure throws a load on the remaining nephrons, producing a sort of osmotic diuresis which tends to cause water depletion. However, neither is water excess well tolerated in such patients or in animal preparations. The osmotic effect was demonstrated by the fact that a well-marked reduction in urine volume occurs in patients with renal failure after reduction in blood urea nitrogen by artificial dialysis. This may be prevented by the addition of urea to the bath and prevention of urea loss. Merrill further found that as the function of a renal transplant improves, less water is excreted by the patient's own kidney, and as the homograft function diminishes, the patient's urine volume increases. Thus the solute load greatly influences the urine volume, particularly in delicately balanced or impaired renal functions. He also showed that the delayed excretion of a water load could be remedied by giving osmotically active substances.

Sodium

In the discussion of acidosis several reasons for *sodium loss* were given. In addition to these, the same increase in load thrown upon the tubules by loss of other nephrons, as mentioned above, may result in interference with the adequate reabsorption of sodium. Sodium retention tends to occur when glomerular filtration rate is impaired without a corresponding diminution in tubular function. Here again poor adaptability does not permit adjustment to either excesses or severe restriction of sodium.

Potassium

In the majority of instances, the chronically damaged kidney handles a normal intake of potassium well. Terminal potassium intoxication, however, is not uncommon, particularly in the presence of a urine volume of less than 500 ml daily. Administration of excess amounts of potassium salts may not be well tolerated. In not too rare instances potassium intoxication may persist over a period of many months, even when the urine volume is good. Potassium deficiency is fairly common in pyelonephritis, because the tubules are injured while the glomerulus remains relatively intact.[13] The same factors as those involved in the loss of sodium apply here. Such patients are merely cation-losers and do not represent examples of true potassium-losing nephritis. Conn believes that pure potassium-losing nephritis is associated with primary aldosteronism, a new entity thus far found only with a specific type of adrenal cortical tumor.[17] Earle, however, disagrees with this.[18] Chronic potassium deficiency may produce a vicious cycle of further potassium loss by damaging the renal tubules and reducing renal function.[19–22]

Phosphate

The inorganic phosphate level seems to depend upon the adequacy of the glomerular filtration rate.[23] Calcium depletion, which is commonly present, stimulates hyperplasia and hypersecretion by the parathyroid glands. This tends to increase the excretion of phosphorus by the kidneys and, if the glomerular filtration rate is not too low, the blood phosphorus may fall to a low figure.[9] If the glomerular filtration rate is below 17 to 20 per cent, increased renal excretion does not occur and the blood phosphate remains elevated.[23]

The blood calcium is usually low because of poor intestinal absorption, a high blood phosphate, and increased excretion of fixed base, including calcium, as a result of inability of the renal tubules to form adequate ammonia or exchange sufficient hydrogen ions to conserve base.[9]

TREATMENT

The intensity of treatment is related to the prognosis. If, during an acute exacerbation of

chronic glomerulonephritis or active pyelonephritis, there is any prospect of improving renal function, then the patient can tolerate a more rigid regimen, because of its shorter duration. In general, glomerular insufficiency produces problems of retention, while chronic tubular lesions usually associated with pyelonephritis present problems of loss. Losses can be made up fairly easily, while retention products often present insurmountable difficulties to the therapist.[13]

The principles of treatment in chronic renal failure are: (1) Minimize protein catabolism, since protein end-products are toxic and are normally excreted by the kidney. (2) Avoid dehydration, since it further reduces renal function. (3) Avoid overhydration, as it may embarrass the heart or cause serious mental and central nervous system manifestations, as well as produce further deterioration in renal function. (4) Avoid Diamox® and acid salts, since the patient is usually already acidotic. (5) Correct acidosis and regulate osmolarity in so far as is consistent with the patient's greatest comfort and well-being. This often has to be accomplished gradually in order to enable the body to make necessary adjustments. (6) Maintain nutrition at a reasonable level. (7) Bring electrolyte concentrations to the levels conducive to the best renal function and body economy. (8) Control undesirable losses of electrolytes from vomiting and diarrhea. (9) Keep appetite and morale in a healthy state.

Water

Water balance is intimately related to the blood sodium level. If water is forced in the presence of hyponatremia, renal filtration is further depressed, water is retained, and water intoxication may develop. Instead of promoting the excretion of solids, the forcing of fluids will reduce it. If salt and water depletion exist, administration of both in proportionate amounts is usually beneficial. Pure water dehydration is unusual in renal failure and may be accompanied by an elevated blood sodium concentration. If the blood sodium level is normal, fluids usually should be forced if properly excreted, since the limited concentrating ability of the tubules increases the water requirement for excretion of a given amount of solids. Water should not be forced in the presence of edema but should be limited to the amount lost through the skin and lungs (about 1000 ml) plus the amount of the previous day's urine volume and any other losses, minus the amount of water formed from food (about 400 ml) daily. Edema may be eliminated slowly by reducing the water intake to 100–200 ml less than this. A similar plan should be followed when cardiac abnormalities are present. Edema must not be eliminated more rapidly than solids can be excreted, because a rise in concentration of these solids may produce serious, or even fatal, disturbances.

Sodium

Aside from water regulation, the management of sodium metabolism requires astute judgment. If the skin is putty-like, indicating dehydration, and the blood sodium is normal, then sodium salts should be used along with water in equivalent quantities as they are found in the blood and extracellular fluid, or about 100 meq of NaCl per liter and about 35 meq of $NaHCO_3$ or sodium lactate per liter. If acidosis is severe, the proportion of $NaHCO_3$ may be increased, but bicarbonate should not be built up too rapidly in the presence of calcium ion deficiency for fear of causing tetany from decreased calcium ionization. If the blood sodium is low, an attempt should be made to decide whether sodium depletion or water excess exists. In renal failure sodium depletion may not present the characteristic findings of the "low salt syndrome"[24] and, if the patient looks well and urine volume is good, sodium is given orally while fluids are restricted. In this way the blood sodium may be built up gradually to normal levels. As the extracellular fluid sodium concentration rises the increased osmotic pressure will extract water from the overhydrated cells so that the blood sodium will increase much more slowly than might be calculated.

If the patient's condition is critical, then intravenous 5 per cent NaCl may be employed. One hundred ml are given first and, if the patient is better, or at least not worse, another

100 ml is administered. If the response is encouraging, 200 ml may be given every 12 hours until the blood sodium is normal. In severe salt losers, more will be needed, but this must be determined by following the 24-hour urine excretion of sodium. If water excess is suggested by the presence of puffy lids or venous distention, then the blood sodium should be brought up by restricting fluids. This should not be done too rapidly, since the concentration of noxious substances will rise along with the sodium concentration. The negative fluid balance in such cases should not be greater than 100–200 ml daily.

If an elevated blood sodium should be present or should be produced in an attempt to eliminate edema in renal failure combined with heart failure, then one must proceed with dehydration, using extreme caution, to give the kidneys a chance to eliminate a proportionate amount of sodium. Otherwise a fatal hypernatremia may develop. A sodium-absorbing resin may be employed to combat hypernatremia. This, however, is a rare situation. Unfortunately, these rules for sodium management are far from infallible and considerable clinical judgment must be used. Some patients seem to do better if the blood sodium is not tampered with. The average patient with renal failure will tolerate neither a severe restriction nor a normal intake of this electrolyte. Three to five grams a day of sodium salts (about 70 meq) are a good starting point. If the patient loses too much weight or becomes dehydrated, the intake of sodium may be increased. *If the blood sodium concentration is normal*, patients may be placed on a diet containing 200 mg sodium (0.5 g NaCl) to determine urinary sodium loss by measuring the 24-hour output daily for several days. After 3 or 4 days the urinary output of sodium will approximate the patient's daily requirement. This does not apply, however, if the blood concentration is not normal, because even with renal failure the loss of sodium will vary with the blood level. By trial and error the physician with a reasonable knowledge of electrolytes can work out a satisfactory compromise between the blood level and the greatest comfort of the patient.

Potassium

Potassium intoxication is usually a terminal problem and occurs after the urine volume falls below about 500 to 1000 ml daily. Not infrequently, however, it does occur in a patient who otherwise is doing well. J. P. Merrill has found that many patients tolerate a blood potassium of less than 6 meq per liter very well. The blood level must be followed carefully, however, and it seems preferable to keep the concentration around 4.5 to 5 meq/lit, since several of our patients have slipped into a critical hyperkalemia rather suddenly when permitted to carry an elevated blood concentration. The blood potassium can be controlled quite well with a sodium cation-exchange resin if the patient can tolerate it orally. The resin removes 1 to 2 meq of K+ per gram of resin,[25] and the dosage varies from 6 to 50 g daily, with the average nearer 6.

Hypokalemia is frequently stated to be unusual in chronic renal failure. Such has not been our experience, particularly in patients with chronic active pyelonephritis without much glomerular damage. These patients are cation-losers and are depleted of potassium as well as of sodium and calcium. The nonprotein nitrogen may remain normal until considerable sodium depletion occurs. A severe tissue potassium depletion with a normal or elevated blood level may be unmasked when hyponatremia and dehydration are corrected. Potassium deficiency causes a deterioration of the renal blood flow and glomerular filtration rate, and causes tubular damage.[19–22] The latter initiates a vicious cycle which may end with the death of the patient. It also produces heart failure, which further disturbs the renal hemodynamics. If the nonprotein nitrogen or urea clearance is normal, potassium can be given in moderate excess with safety, but if glomerular damage is exhibited by a considerable nonprotein nitrogen elevation, the potassium dosage must be very carefully adjusted by following the blood values until they are stabilized on a regular dose. Some potassium-losing nephritic patients may require administration of as much as 24 g of potassium chloride daily,[26] but Conn believes that such cases are caused by aldosterone-

producing tumors. Such cases should be associated with elevations of blood sodium and blood carbonate.[17] In ordinary cation-losers 5 to 10 g of added potassium salts are usually sufficient and cation-losers have a *depressed* blood sodium and carbonic acid.

Calcium

Blood calcium may remain normal for some time, despite considerable elevation of the blood phosphorus. Eventually, however, it becomes depressed in most instances, for reasons mentioned above and for some which are not understood. In patients with glomerular insufficiency, hypersecretion by the parathyroids is not able to bring the blood phosphorus to normal.[9] The only way that the calcium concentration can be raised is through promoting elimination of phosphate in the stool by giving 100 to 150 ml of a liquid aluminum hydroxide preparation (or 20 to 30 tablets) each day.[31] Calcium salts administered orally are not effective in hypocalcemia except as follows: Patients with relatively pure tubular insufficiency, as in Fanconi's syndrome or Milkman's syndrome (with pseudofractures), will have a normal or low blood phosphorus; the level of blood calcium can be raised by correcting the acidosis with sodium bicarbonate or sodium lactate and administering calcium gluconate, 3 to 6 g daily, along with vitamin D, 25,000 to 50,000 units daily. After the blood concentration has been normal for several months the calcium and vitamin D can probably be discontinued, provided the blood carbonate is kept normal.

If the patient with renal failure has radiologic evidence of nephrocalcinosis or, if the blood calcium is nearly normal or high, and the phosphorus normal or low, one must consider the possibility of (1) hyperparathyroidism, (2) ingestion of excessive amounts of milk and alkali,[27] or (3) hypervitaminosis D[28] (100,000 to 300,000 units per day). Myeloma and sarcoidosis may also cause nephrocalcinosis but will not be considered here. Any one of these may cause pure tubular damage; removal of the parathyroids in one instance and correction of the diet in another may permit return of renal function to normal.

Other Electrolytes

The low serum chloride is probably of no importance provided acid-base balance is not disturbed.[29] It would seem that sulfate should be bound by aluminum hydroxide in the intestines, but the author has seen no report on this.

Protein

If protein catabolism could be eliminated, the problems of chronic uremia could all be solved. This is obviously out of the question, however, since a certain amount of endogenous protein catabolism goes on constantly and there are also losses from proteinuria in renal disease and dermal erosion.

A few groups have advocated high protein intakes, but this has found little favor. Able observers and investigators differ widely as to the optimum intake of protein, and it must be said here that proof is lacking to support any group at the present time. Certain suggestive evidence, however, has been brought forth, and this will constitute the subject of this discussion. Burnett[30] has serious doubts as to the value of any protein restriction below one gram per kilogram of body weight. His observations on the "laissez-faire" technique in the management of chronic renal failure have led him to believe that patients, if left alone, will gradually determine the proper amount of protein for themselves, by effects of appetite on the one hand and nausea on the other. He even believes that some of the chemical abnormalities in renal failure may be compensatory and that correction may lead to deterioration of renal function. The other extreme of 0 to 20 or 30 g of protein daily is supported by Borst,[32] Kolff,[33] and Kempner.[34] An intermediate position for the use of 0.5 g of protein per kilogram daily is taken by J. P. Merrill.[31]

The ideal amount of protein would seem to be that which produces the minimum excretion of nitrogenous material without provoking a rise in the blood level of protein catabolites. At first glance it might seem that the lowest possible protein intake might accomplish this. An excellent refutation of this position has recently been presented.[31] Some of this evidence, plus some added material, constitute the following discussion.

The problem of protein intake can be approached from several different directions: (1) by determining the quantity of protein catabolites in the urine on various diets in normal people. While some information can be gleaned from this, it is not comparable to the effect of diet upon patients with renal disease. (2) By measuring the level of protein breakdown products in the blood and in the urine in uremic subjects on various diets.

TABLE I

Treatment of Uremia with a Butter, Sugar, and Cornstarch Diet*

	Amount	Carbohydrate	Protein	Fat	Sodium	Calories
	g or ml	*g*	*g*	*g*	*g*	
Sugar	150	150				600
Butter	100			81	0.98	729
Cornstarch	150	130.5	0.75	0.3	0.006	525
Water	1500					
Total		280.5	0.75	81.3	0.986	1854

* From Borst.[32]

The first method has been applied by several authors. In total starvation, the otherwise normal individual excretes from 6 to 8 g of nitrogen for the first few days. From that time until about the twenty-sixth day, he excretes about 4.3 g and after that only from 2 to 3 g.[35] When no protein is given but instead 300 g of glucose and 100 g of fat are added, the nitrogen output falls to as low as 1.22 g per day.[36] When a small amount of protein is added, as in the "rice and fruit juice" diet, which contains 20 g of protein daily, Kempner found that N excretion fell to as low as 2.26 g per day.[34] This nearly but not quite achieves N balance.[37, 38] Less accurate data are available on the second approach to this problem, but Borst[32] has treated some patients with uremia on a butter, sugar, and cornstarch diet (Table I) with favorable results, as has Kolff.[33] Obviously these diets can reduce protein catabolism to a very low level, low enough so that the kidneys of many patients with renal failure are able to keep pace or even gain a little.

Why not then eliminate protein from the diet? Merrill[31] says emphatically "no" and gives the following reasons: (1) while protein is not stored, it is constantly being replaced[39] and a certain amount is converted to carbohydrate for energy.[40] Under stress following injuries nitrogen loss may be as much as 7.7 per cent of total body nitrogen and greater than the nitrogen content of the entire liver.[41] The purpose of this could be to supply easily available building blocks for damaged tissue.[42] Losses from proteinuria and skin losses must be replaced. The minimum protein requirement for "wear and tear" replacement is about 0.5 g per kilogram of body weight, and to this must be added any abnormal losses. (2) Protein is needed for the formation of creatinine, ammonia, certain hormones, for blood loss replacement, antibodies, and finally, sulfur from protein is required to detoxify phenols. (3) Protein deficiency may possibly contribute to weakness, anorexia, and loss of weight.

The type of protein is of great importance. The ideal protein is one which will be employed maximally in the building and repair of cells, leaving a minimum amount for excretion by the kidneys. Such a protein must contain all of the essential amino acids (Table II). These

TABLE II

Minimum Daily Requirement of Essential Amino Acids*

Essential Amino Acids	Minimum Daily Requirement
	g
L-Tryptophan	0.25
L-Phenylalanine	1.1
L-Lysine	0.8
L-Threonine	1.0
L-Valine	1.6
L-Methionine	2.2
L-Leucine	1.1
L-Isoleucine	0.7

* After W. C. Rose: *Physiol. Rev.* 19: 109, 1938.

proteins are spoken of as having a high biological value. Another important fact is that all of the essential amino acids must be eaten simultaneously, or none of the others can be utilized for cell-building and instead will be converted to carbohydrate for energy.[43] A pure vegetarian diet can support normal health and development, although weight and physique in adolescents on this diet are poor,[44] and hemoglobin is low.[45] But, except for soybeans,[46] animal proteins have a much higher biologic value than vegetable proteins.[47,48] However, the phosphorus content of animal protein is much higher than that of vegetable protein,[49] although phosphorus can be eliminated through the stool by using aluminum hydroxide. The sulfur content of both animal and vegetable proteins is about the same.[49] Therefore, one is forced to the conclusion that, in the light of our present knowledge, 0.5 g per kilogram of *animal protein*, plus enough to replace urinary losses, is to be preferred. The chief theoretical objection is that the end products of animal protein digestion are acid, whereas those of fruit and vegetables are alkaline. The animal protein diet has been tested in normal individuals and has been found to reduce the excretion of protein catabolites,[50] but the diet must be tested more carefully in patients with renal failure. It may be that other objections can be uncovered. It is also possible that protein can be used more efficiently if the intake is lowered to as little as 0.3 g per kilogram, as suggested by the finding of gradual reduction in nitrogen excretion mentioned above during starvation or on the Borst or Kempner diet.

Carbohydrate

While Gamble[40] showed that elevation of carbohydrate intake above 100 g a day had little additional protein-sparing effect (that is, reduction in the use of protein by the body for energy needs), his experiments were designed for a short-term life-raft ration. As longer studies have shown (see above), nitrogen excretion can be reduced even further with more carbohydrate, and since there is no contraindication to a liberal amount of carbohydrate, a normal intake is desirable. At least 100 g a day is necessary to prevent acidosis and from 300 to 400 g a day are not excessive in the azotemic subject if he will take it. In the diabetic patient with intercapillary glomerulosclerosis, this may have to be reduced considerably, since careful control seems to be important in such cases.[51]

The carbohydrate should be ingested simultaneously with the protein, as this greatly improves the utilization of the amino acids.[52]

Fat

For the average patient with uremia, a diet of about 2000 to 2500 calories will suffice, and with 35 g of protein and 300 to 400 g of carbohydrate, this leaves about 800 to 1000 calories to be supplied by fat. Fat is valuable because it supplies 9.3 calories per gram instead of the 4.1 supplied by carbohydrate. It is also necessary to the well-being of animals,[53] though it is apparently not essential in man, since human volunteers were fed a fat-free diet for six months without production of symptoms.[54] Fat also diminishes the specific dynamic action of protein and carbohydrate,[55] possibly by slowing absorption and enabling the body to utilize them more efficiently. On a reduced protein intake, fat holds the loss of protein to "wear and tear" level in rats, whereas this was not possible without it.[56] In six-day experiments in man, a protein-sparing action over and above that of carbohydrate was shown.[57] Meng has demonstrated a 30 per cent increase in the protein-sparing action of carbohydrate by the intravenous administration of fat.[58] The palatability of a diet is greatest with a fat intake of around 80 g. The proper proportion of fat in the diet is probably between 33 and 50 per cent of the caloric intake.[59] Larger amounts may produce nausea and flatulence. Also, since many patients with renal failure have hypertension and vascular disease, the administration of larger amounts of fat over a long period of time seems inadvisable.

At the beginning of treatment, when renal failure is well advanced, a protein-free diet may be of value for a short time to bring the patient to a better state, after which the steady state may be maintained with a less rigid diet. The Borst diet (Table I) is an

example of a suitable no-protein, low salt, normal carbohydrate and fat diet. It is more applicable to the patient with acute renal failure in whom salt is not desirable; salt may have to be added for the patient with chronic renal failure. If tube feeding is necessary, the Bull diet[60] of peanut oil and dextrose may be employed, but, again, this is feasible for only short periods. At times, if carbohydrate and fat supplements are desirable, the proprietary preparations of Ediol® (coconut oil and dextrose—5 calories per ml) per or Lipomul® (peanut oil and dextrose —4 calories per ml) may be given after meals.

SUMMARY

Chronic renal failure affecting chiefly the glomeruli produces problems of abnormal retention of substances, whereas chronic tubular disease produces deficits principally of cations. The latter is simpler to treat, although there is a lack of adaptability to either deficits or excesses.

Water intake should be high unless water retention or edema is present. Forcing fluids in the presence of edema will cause deterioration of renal function. The salt intake should average about 4 or 5 g daily. The salt intake should be reduced with water retention, but few patients will tolerate rigid restriction. Massive amounts of salt may be required in unusual instances.

Potassium abnormalities are treated as indicated by the blood level and excretion studies. Patients with plasma potassium levels above 5.5 meq/liter should either be watched very carefully or treated with a potassium-absorbing resin.

Calcium deficiency without blood phosphorus elevation responds well to oral administration of calcium, vitamin D, and alkali administration (after milk-alkali administration, vitamin D intoxication, and hyperparathyroidism have been ruled out). If the blood phosphorus is high, these measures are futile and phosphorus has to be eliminated with aluminum hydroxide.

The diet should contain about 0.5 g per kilogram of body weight of animal protein daily, supplied by a protein of high biological value, about 3–4 g per kilogram of carbohydrate, and 1–1.5 g per kilogram of fat. (See Appendix, Table III.)

APPENDIX

TABLE III

Menu for Diet Containing Approximately 2200 Calories, 50 Grams Protein, and 4 Grams Salt*

Breakfast
- 1 large glass fruit juice or large serving fruit
- 1 slice toast with 1 teaspoon butter and 1 tablespoon jelly
- 1 serving cereal (hot or cold) with 3 oz heavy cream and sugar
- 1 egg with 1 teaspoon butter
- Tea or coffee with cream and/or sugar

Before lunch: 4 ounces sherry

Lunch
- Sandwich
  - 2 slices bread
  - 1 ounce meat
  - 1 teaspoon butter
  - 1 teaspoon mayonnaise
- Tossed salad with 2 tablespoons French dressing
- Large serving fresh or canned fruit
- Tea, coffee, or carbonated beverage

Before dinner: 4 ounces sherry

Dinner
- 3 ounces meat with gravy
- 1 average serving potato with 1 teaspoon butter
- 1 serving vegetables with 1 teaspoon butter
- Vegetable salad with 2 teaspoons mayonnaise
- Large serving fresh or canned fruit
- Tea, coffee, or carbonated beverage

Bedtime
- Large glass fruit juice or carbonated beverage
- 2 graham crackers with 1 tablespoon jelly

TABLE III (cont.)

Food	Carbohydrate	Protein	Fat	Sodium
	g	g	g	mg
1 large fruit	10	—	—	2
1 slice toast, regular	15	—	—	170
1 t† butter	—	—	5	50
1 T jelly	6	—	—	—
1 serv. cereal	15	2	—	10
3 oz heavy cream	—	—	30	36
1 t sugar	5	—	—	—
1 egg	—	7	5	40
1 t butter, regular	—	—	5	50
1 oz light cream	—	—	5	9
1 t sugar	5	—	—	—
4 oz sherry	17	—	—	—
2 slices bread, regular	30	4	—	340
1 oz meat	—	7	5	20
1 t butter, regular	—	—	5	50
1 t mayonnaise	—	—	5	90
Tossed salad	—	—	—	9
2 T French dressing	—	—	10	—
Large fruit	20	—	—	2
Carbonated bev.	10	—	—	—
4 oz sherry	17	—	—	—
3 oz meat	—	21	15	60
2 T gravy	—	—	10	—
1 serv. potato	15	2	—	1
1 t butter	—	—	5	50
1 serv. vegetable	7	2	—	9
1 t butter, regular	—	—	5	50
Veg. salad	—	—	—	9
2 t mayonnaise	—	—	10	180
Large fruit	20	—	—	2
Sugar (tea)	5	—	—	—
Large fruit	20	—	—	—
2 crackers	15	2	—	—
1 T jelly	6	—	—	—
Totals	238	49	120	1239

* Salt may be used sparingly in cooking and none to be added at table. A salt content of 4 g is given only as an example, since, as noted in the text, patients with renal failure may require a high salt intake. This must be individualized and may be increased by table salt and other sodium supplements without increasing protein content.

† T—tablespoon; t—teaspoon. (Total Calories 2293.)

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Nutrition and the Nephrotic Syndrome in Adults

By JOHN R. SQUIRE, M.D., F.R.C.P.*

THE NEPHROTIC syndrome is encountered in a variety of diseases which lead to considerable and prolonged proteinuria. The need for special diets has long been appreciated, but only gradually have the various characteristics of the syndrome been recognized. Some of these provide a reasonable basis for the forms of treatment now recommended, others are still poorly understood, and a short account of the clinical and biochemical features of the syndrome will be given. Varying degrees of malnutrition are encountered and the problem of how to assess the individual patient will also be discussed before dietary control is considered in detail.

Edema, considerable proteinuria, and hypoalbuminemia constitute the prime essentials for diagnosis, as described in various reviews.[1–5] In adults, the condition usually develops when daily losses of protein exceed 10 g; in severe instances, 20 or even 30 g are lost each day. These losses continue for many months unless checked by treatment, and appear to be the main determinant of the fall in serum albumin concentration. Thus with losses of 10 g daily, the serum albumin concentration falls at least to half of the normal (normal = 4 g/100 ml), and edema is likely unless the salt intake is drastically reduced. With losses of 20 g/day, the serum albumin usually falls below 1 g/100 ml; at this level in adults, the development of edema can seldom be prevented.[5]

As previously described,[4] the serum of nephrotic patients also shows other changes the extent of which can be correlated with the serum albumin concentration or with the amount of protein lost in the urine. These changes include reduction in α_1- and γ-globulins, both of which are found in the urine, and increases in α_2-globulin, β-lipoproteins, and in fibrinogen—all large proteins which are lost comparatively little through the glomerular filter. Increases in serum cholesterol and other lipids are often marked. Their concentrations are not so closely related to urinary protein losses, and the causes of their accumulation in the blood are not fully explained. As would be expected from their small molecular size, the metal-carrying globulins (transferrin and ceruloplasmin) are also lost in the urine together with iron and copper, and their serum concentrations are reduced.[6,7] These biochemical findings serve to characterize the syndrome, for they differ considerably from those in other forms of hypoproteinemia.

A moderate degree of orthochromic normocytic anemia is usually present. In periods when edema is forming, this may be obscured by a reduced plasma volume. The anemia is usually due to under-production of erythrocytes, though in some forms of rapidly progressing renal disease,[8] increased red cell destruction can be demonstrated.

Significant retention of non-protein nitrogen is not a feature of the syndrome, creatinine clearances being most commonly in the range 25 to 75 per cent of normal. Control of serum electrolyte concentrations is usually well maintained, though sodium and potassium concentrations are often at the lower limits of normal. The serum calcium is often in the range of 8 to 10 mg/100 ml; with severe hypoalbuminemia this may not represent any significant change in the concentration of ionized calcium. The serum phosphorus is usually within normal limits.

From the Division of Pathological Studies, University of Birmingham, England.

* Leith Professor of Experimental Pathology, and Director of the Division of Pathological Studies, University of Birmingham; Consultant, Metabolic Research Unit, Little Bromwich Hospital, England.

NUTRITIONAL STATUS

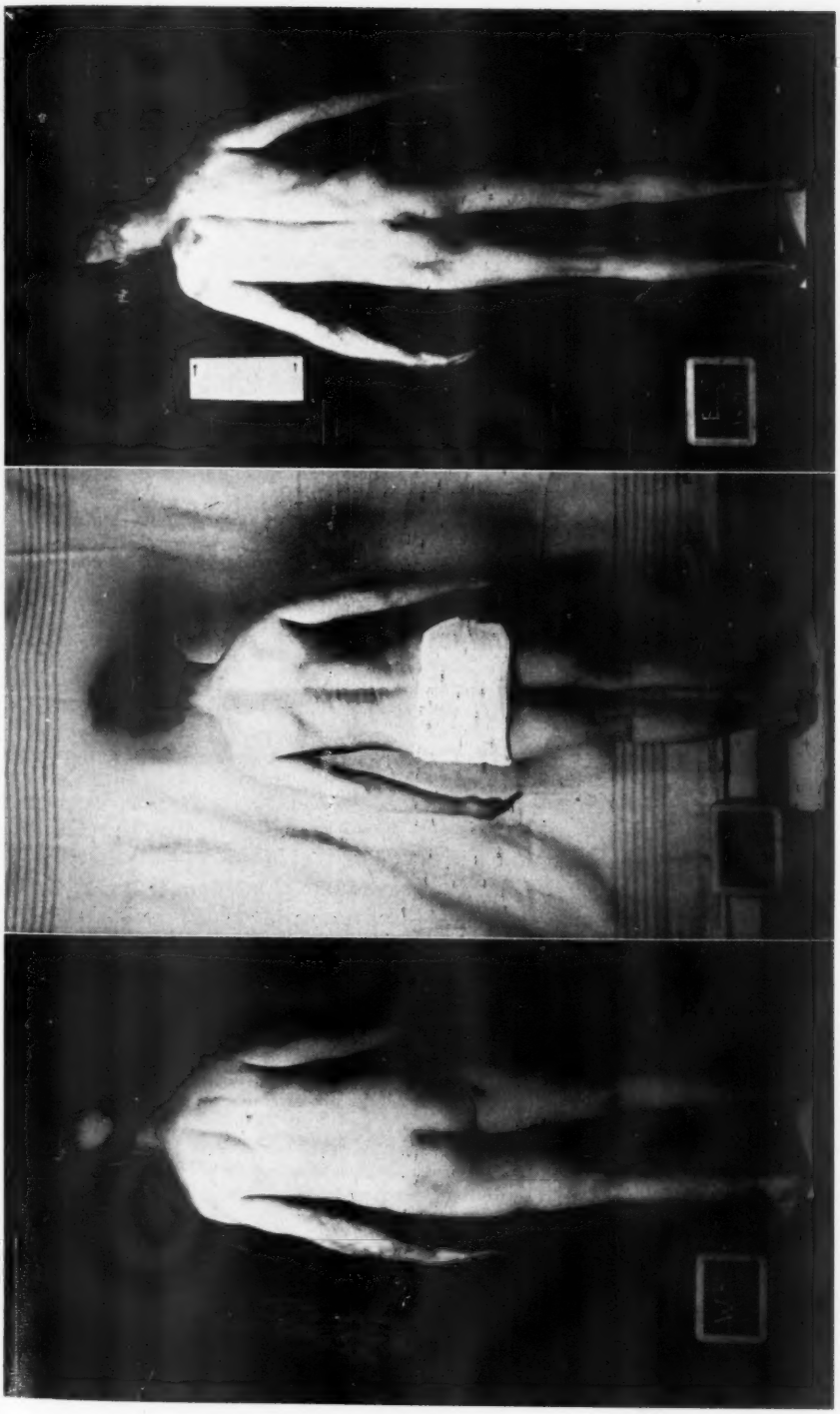
The nutritional status of the nephrotic patient on admission to hospital is variable, depending on the length and severity of the illness and on the previous diet. With such a chronic illness, often involving loss of appetite and sometimes bouts of diarrhea, considerable depletion of body nitrogen is often present. As a rule, this cannot be demonstrated on clinical examination when edema obscures the musculature of much of the body. Further, the thickness of subcutaneous fat is not reduced as judged simply by pinching it up or by more exact caliper measurements at various sites. The results of long-continued nitrogen balance studies are, therefore, surprising, since they prove that gross depletion occurs and can be steadily remedied by an appropriate diet. This has been shown by a number of workers[9–11] and never denied. Blainey,[12] for instance, has found cumulative positive nitrogen balances of 240 g, 312 g and 488 g of nitrogen in three patients studied for periods of from 36 to 99 days; the standard body weights of these patients were 45 kg, 85 kg, and 55 kg, respectively.

Other forms of nutritional deficiency are not evident apart from anemia. Nail and tongue changes characteristic of specific forms of deficiency are not found, nor is there clinical evidence of vitamin deficiency. Rarely, yellow lipid is deposited in skin creases (such as the antecubital or popliteal fossae), but this seems only to be associated with extreme hyperlipemia.

Since repeated accurate nitrogen balances constitute a specialized form of investigation, special consideration must be given to some simpler means of determining the presence of body protein depletion. Both simple biochemical and clinical criteria require scrutiny. By estimating from time to time the total nitrogen content of 24-hour specimens of urine, low outputs of nitrogen (e.g., 5–10 g N/day) can be demonstrated, in spite of the urinary losses of protein, even when very high protein intakes have been given. The outputs of urea are especially low. As with complete nitrogen balance studies, these determinations serve to show that nitrogen storage is proceeding, for with a correspondingly high intake of protein, the normal person would soon increase the urea output. In contrast with the low urea output, the creatinine excretion is not reduced. The reduction in albumin and other serum proteins, even allowing for a diminished plasma volume, only accounts for a small proportion of the total protein deficit. Tissue enzyme studies similar to those described by Waterlow[13] in malnourished African children have not yet been applied to nephrotic patients. At present, therefore, the only satisfactory biochemical test remains the daily measurement of nitrogen repletion by means of balance studies.

CLINICAL APPEARANCE

Clinical examination after the loss of edema may reveal striking muscular wasting. This was described by Peters and Bulger,[11] and is illustrated in Figure 1(c). Though evident to some extent in the muscles of the shoulder-girdle and trunk, it is particularly well seen in calves and thighs. This patient, E.S., had been severely ill for 15 months; abdominal paracentesis had been performed on many occasions, and he had experienced attacks of cardiac asthma. His diet had been poor except for a few weeks in the hospital prior to the loss of his edema, which followed the administration of cortisone. For comparison, patient W.H. is shown in Figure 1(a), a man similar in age and height to E.S. But W.H. had been ill for three months only, and had been engaged in heavy manual labor up to the time of his illness. The photograph was taken soon after the loss of 10 kg body weight with the loss of edema. The patient in Figure 1(b) was intermediate in nutritional status. Though he had suffered from heavy proteinuria for four years, with edema for much of this time, when photographed he had received special dietary treatment for the preceding five months with repletion of more than 300 g of nitrogen. Qualitative tissue changes indicative of protein depletion were absent in W.H. and C.D. Defective growth of scalp and body hair was noted in E.S. during the period of severe illness. In many patients previous periods of poor nail growth are evident when, in convalescence, transverse



(a) W. H. No wasting of muscles or fat. Age 52. (b) C. D. Some muscular wasting; some excess of subcutaneous fat. Age 22. (c) E. S. Marked muscular wasting; normal amount of fat. Age 51.

All patients were photographed soon after loss of edema. For comparison with Figure 2.

Fig. 1. Tissue wasting in nephrotic patients—visual evidence.

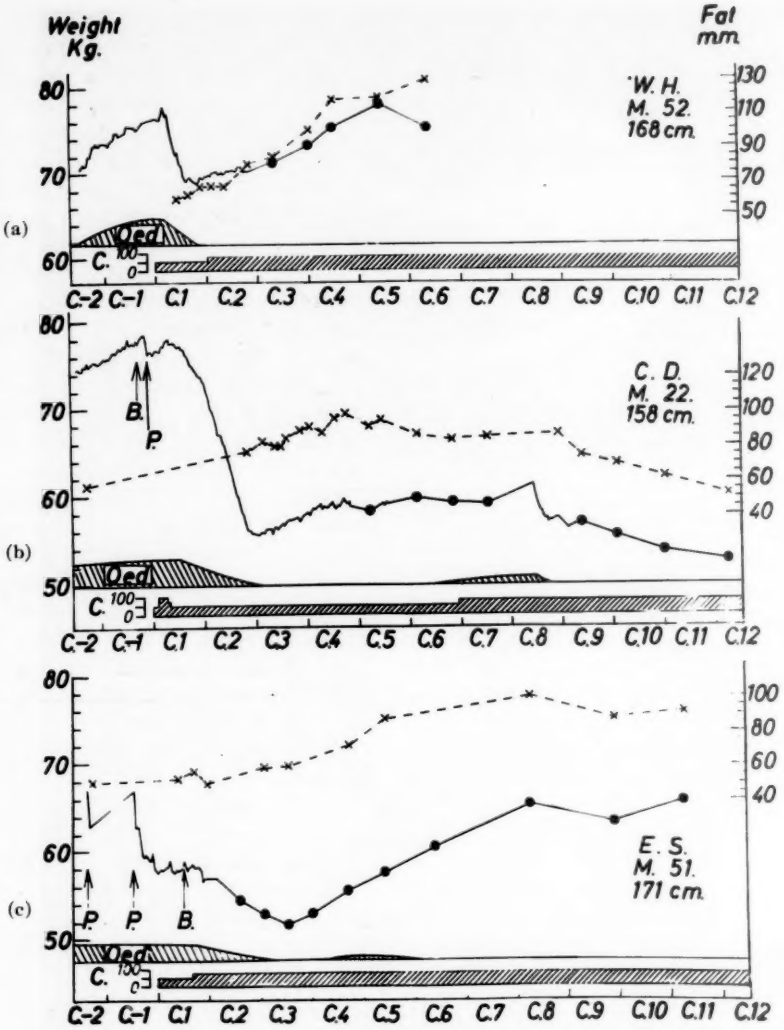


Fig. 2. Tissue wasting in nephrotic patients—quantitative evidence.

Comparison of body-weight (continuous wavy line daily readings; black circles joined by straight lines out-patient readings) with summed caliper measurements of subcutaneous fat at 9 sites (dotted lines joining crosses). Scales as shown, increase of 5 mm fat thickness plotted as approximately equal to 1 kg weight of fat. In each case 60 mm fat (average normal at age 30) is aligned with normal body-weight at age 30 corresponding with patient's height. Horizontal scale—months, numbered according to start of cortisone treatment (C)—dosage as shown. Oed. = edema, graded from clinical records. P = paracentesis. B = blood transfusion.

(a) Correspondence of fat and body weight in W. H. when edema free, subsequent disproportionate increase in fat with cortisone and return to light work only.

(b) Moderate depletion of body substance other than fat (which is excessive) in C. D. Subsequent increase in obesity, which was lost with some improvement in relative position of body-weight after starting work in C.9; also slight recurrence of edema in C.8.

(c) Gross depletion of tissues other than fat in E. S. Subsequent obesity as shown by rise in fat measurements; relatively greater rise in body-weight, showing that fat-free body substance has also increased.

ridges can be seen some distance from the nail bed.

An attempt has been made to translate these qualitative clinical impressions into a more exact quantitative assessment by considering the body weight after allowance for the thickness of subcutaneous fat in each patient. As Edwards has shown,[14] the fat in all body regions increases proportionately as obesity develops, and falls as it diminishes. The amount of subcutaneous fat can therefore serve as an approximate measure of the total body fat. Skin-fold thicknesses have been measured by Dr. R. F. Fletcher[15] using calipers of the design described by Edwards.[16]

Triplicate readings are taken weekly on in-patients and at all subsequent follow-up attendances of nine sites in the upper parts of the body to minimize interference by edema. The sites include the upper arm, neck, the back and front of the chest, and correspond fairly closely with those designated by Edwards[14,17] as "A2, B2, D3, AF1 and AI1," all but the first being bilateral measurements. By routine use of the method on all patients in the Metabolic Unit for a period of 18 months, the general validity of the method has been checked and its clinical value established. Important sources of error remain and will be discussed fully elsewhere;[15] no allowance has been made for variations in skin thickness; small differences in individual fat distribution are found and more reliable allowances for the effects of height in males are required—provisional calculations given here are partly based on Edwards' measurements[14] which were made in females.

In Figure 2, the fat-fold thickness measurements are plotted in relation to the body weights of the three patients illustrated in Figure 1 when edema had been lost. The relative scales for the sum of the skin folds ("fat") and for the "weights" have been chosen so that with normal nutrition or ordinary obesity, the fat- and weight-curves should superimpose. Depletion of body substance other than fat should then result in the weight-curve lying below the fat-curve. On the other hand, excess of other body substances, e.g., edema, cause the weight-curve to lie above the fat curve, as seen in C.D. during the months C-2, C-1, C1, and C2. Evidently, W.H. when first free from edema, i.e., in month C2, showed no evidence of body protein depletion on this basis, his slight obesity being matched by a weight of 71 kg. At the other extreme, E.S., though not deficient in subcutaneous fat, was grossly depleted in other tissues when first edema-free (month C3). By subtraction of the weight- from the fat-curve, this depletion can be calculated as amounting to some 18 kg. C.D. occupies an intermediate position. Having some excess of body fat, his weight when edema-free (C3) was not below the average normal for his height and age. Nevertheless, a definite deficiency of body tissue other than fat must still have been present, amounting to about 8 kg in body weight. The excess of body fat also explains the difficulty in appreciating any muscular wasting in Figure 1(b). The subsequent course of the curves in Figure 2 will be discussed below in relation to diet and cortisone therapy. This method of assessment is thought to be correct in principle, though capable of much improvement in detail. Though obviously much less accurate than nitrogen balance studies, it has the advantage of allowing a definite assessment to be made as soon as edema is lost; eventually, with further experience, it should lead to useful prognostic statements, indicating how long each patient may need the special forms of diet now to be considered.

Until recently, conservative treatment with special measures to eliminate or reduce edema was the best prospect the nephrotic patient could be offered, except in occasional instances when the cause of the proteinuria could be established and eliminated (e.g., adherent pericardium,[18] chronic pyelonephritis). In ordinary circumstances, insuring that each patient received (and ate) an optimal diet was of prime importance. Many patients are now best treated by the very long-continued administration of cortisone (or of a related drug) in moderate dosage. To expedite convalescence and to avoid the complications associated with this form of therapy, a suitable diet still remains essential.

DIETARY MEASURES FOR CONTROL OF EDEMA

The sodium concentration in nephrotic edema fluid is about 130 meq/liter and the chloride concentration is about 110 meq/liter, most of the remaining anions being in the form

of bicarbonate. These values are based on analysis of samples withdrawn by paracentesis; the sodium and chloride values are also consistent with the results of balance studies during diuresis.[19] When edema is increasing, its progress can be slowed by limitation of sodium intake. With special dietary facilities, intakes can be reduced to 10–15 meq of sodium and 20–25 meq of chloride daily, while maintaining protein intakes of about 150 g. Under these circumstances, the nephrotic patient may excrete less than 1 meq of sodium in the urine daily. Allowing for losses of 1–3 meq of sodium in the stools, about 9 meq of sodium may then be retained within the body. The maximum rate of edema formation is then 9 × (1000/130) = 70 ml daily, if the sodium content of the plasma remains constant and regulates the interstitial fluid concentration at about 130 meq/liter. This constancy of plasma sodium is usually well maintained. Occasionally the plasma sodium concentration falls, presumably as a result of unusually severe tubular damage; considerable rises in blood urea may then occur until more sodium is given in the diet.

When the nephrotic patient retains, say, 9 meq of sodium he also retains 8 meq of chloride. Thus, on a diet containing 22 meq of chloride, the urinary losses of chloride amount to about 10 meq, with 3 meq being lost in the stools. Plasma chloride concentration, like that of sodium, remains well controlled. Administration of mercurial diuretics may lead to a fall in plasma chloride concentration which is gradually restored, even on low intakes.

Potassium Status

Although sodium and corresponding amounts of chloride are retained during edema formation, potassium excretion is regulated in a normal fashion at all stages of the nephrotic syndrome. It is usual for a high protein diet to contain about 80 meq of potassium daily. This amount of potassium appears to be adequate for any possible rate of tissue replenishment, or for the prevention of potassium depletion during the administration of cortisone in moderate dosages.

Water Intake

In theory, edema formation might be limited by restriction of water intake, though no doubt cellular dehydration would result. On admission to the hospital some patients are found to have been practicing water restriction, either on medical advice or on their own initiative. Increasing the water intake of such patients by 1–2 liters daily appears to cause no substantial prolonged increase in weight, and subjective improvement often results. In grossly edematous patients, an additional test load of 1 liter of water, taken rapidly, is not eliminated in as short a time as in normal subjects, but is all excreted within 48 hours. A free fluid intake, with a minimum of 1.5–2 liters, is therefore usually recommended.

Sodium Restriction

Very low sodium diets (10–15 meq) are unpalatable, though most adult patients become accustomed to them. Without expert dietetic assistance, diets containing 30–40 meq can be arranged, though these are scarcely less unpalatable. In severely affected patients, the more rapid gains in edema with these larger intakes of salt may lead to the necessity of performing paracentesis more frequently.

The question whether a sufficiently balanced diet is obtainable with severe restriction of sodium is perhaps of greater importance. The use of milk, rendered "sodium-free" by dialysis, ion-exchange, or other methods, has greatly increased the ease with which a satisfactory high protein, low sodium diet can be constructed. Patients receiving 150 to 200 g of protein daily obtain about half of this in the form of milk powder. This also ensures a good intake of calcium and phosphorus. In many countries, dried whole milk is available in "salt-free" form with added potassium and carbohydrate. In some cities of the United States, sodium-free fresh milk is available.[20] "Salt-free" skim milk or casein preparations are also available, and these may be useful if a high protein, moderate fat intake is considered necessary.

Sodium restriction should be regarded purely as an emergency measure to lessen edema formation during the more severe period of the

illness, when heavy proteinuria and extreme hypoalbuminemia is present. Reduced proteinuria is often followed by the elimination of edema, and after the peak of diuresis has been passed, plasma albumin concentrations tend to rise. At this stage, test doses of additional sodium chloride (e.g., 50 m mol) can be given. If corresponding amounts are eliminated in the urine within 24 hours, gradual increases in salt intake are then permitted, with the proviso that restriction may be re-instituted if edema tends to recur. There is no evidence that salt is in any way harmful to the *convalescent* nephrotic patient; indeed, the gradual return of salt to the diet may give a boost to morale, much needed after a tedious illness. In physiologic terms, the kidney, presumably under the influence of aldosterone, has been conserving sodium in order to minimize plasma volume depletion; during convalescence with larger amounts of circulating albumin, the plasma volume has regained a more normal level; the liberation of aldosterone is then reduced, and the kidney is allowed to excrete salt in accordance with the intake.

Other Minerals

It is convenient to discuss at this point the requirements of the nephrotic patient for other minerals. Urinary losses of iron and of copper are increased as the metal-carrying globulins are included in the proteinuria.[6,7] But attempts to cure the anemia of the nephrotic syndrome by administration of these metals have not succeeded. On the other hand, restoration of normal hemoglobin levels are seen when cortisone and a high protein diet are given daily. Apparently, therefore, hemopoiesis is not limited by shortages of iron or copper when a good diet is being eaten.

OPTIMAL INTAKES OF PROTEIN AND CALORIES

While there is general agreement that nephrotic patients require more protein than the average hospitalized patient, there is much doubt about the optimal intake of protein. The importance of suitable carbohydrate and fat intake, though stressed by such authorities as Peters and Bulger,[11] often escapes attention. These differences of practice stem mainly from the lack of reliable data on which to base a proper choice. Although it is nearly 40 years since Epstein broke away from current views that nephrotic states, like other renal conditions, should be treated by low protein intakes, very few exact studies have been made. As already noted, nitrogen balance data are needed to evaluate different forms of diet for nephrotic patients; they have been used by Peters and Bulger,[11] Keutmann and Bassett,[10] Liu and Chu,[21] Farr,[9] and by Blainey.[12]

Peters and Bulger[11] studied six patients with nephritis and edema. Careful balance studies were maintained for periods of between 8 and 92 days. Protein intakes were not high, varying from about 50 to 80 g daily (0.10 to 0.19 g N/kg/day) and calorie intakes were varied between 2000 and 3500 (from 30 to 55 calories/kg/day). Nevertheless, the conclusions from this very careful work form a natural starting-point for further investigations. Peters' patients were often in negative or zero nitrogen balance on intakes of less than about 0.12 g N/kg/day. Increasing the intake by 0.04 g N/kg/day resulted in positive balances equivalent to about 80 per cent of this extra protein when calorie intake was simultaneously raised from 49 to 55 calories/kg/day. Although Peters is careful to point out that comparisons between different patients are not always justified, the importance of the high calorie intake seemed to be underlined by the smaller positive nitrogen balance in another patient receiving more protein (0.18 g N/kg/day) with only 40 calories/kg/day. Stress was also laid on the surprising degree of emaciation evident after the loss of edema, and the long-continued positive nitrogen balances which could be maintained by suitable diets.

Liu and Chu[21] studied two patients for prolonged periods in Peiping. Both patients were edema-free at the time of the balance studies. Their body weights increased by 5.1 kg in 84 days and 8.7 kg in 105 days, respectively, and the corresponding cumulative nitrogen balances amounted to 55 g and 83 g N, respectively; so that approximately 90 g body weight were gained for every 1 gram of nitrogen. This seems to imply that these two patients

gained much more fat than "flesh" (i.e., protein-containing tissue which contains 3–4 per cent nitrogen). For more than half of the period of treatment in each case, the protein intake was only moderate (0.27 and 0.22 g N/kg/day) with calorie intakes varying between 33 and 86 calories/kg/day. This work showed that at least in the early stages of treatment of depleted patients, it was possible to maintain some degree of positive nitrogen balance on these moderate protein, high calorie diets, and that on the higher calorie intakes, more strongly positive balances were obtained. But a time element was also demonstrated; in the later periods, smaller balances were obtained than in earlier periods with identical diets. At this stage, larger positive nitrogen balances were obtained when protein intake was increased without alteration in calorie intake. From this work, it is not possible to define the optimum protein intake—in one case (a 55-kg man) it appeared to be 175 g/day, in the other (a 30-kg youth) the largest positive nitrogen balance occurred on an intake of 75 g protein daily. But the time element noted above prevents detailed conclusions being valid, since the highest protein intakes were given toward the end of the experiment.

OTHER STUDIES

Keutmann and Bassett[10] studied three patients suffering from Bright's disease with heavy proteinuria; in two of these, very careful studies were made with the special facilities of a metabolism division. In each case a basal diet was constructed containing about 0.11 to 0.18 g N/kg/day. For varying periods, supplements of mixed protein, lactalbumin, egg white, serum protein or liver residue protein were added to give intakes of up to 0.4 g N/kg/day. Calorie intakes were also varied in the second patient between 30 and 50 calories/kg/day, the first patient being maintained on about 40 calories/kg/day. Since it was observed on occasion that proteinuria was increased after some time on the higher protein intakes, separate calculations were made of the protein "deposited" within the body and of the total protein "synthesised," i.e., that "deposited" plus that lost in the urine. High rates of deposition were obtained when high protein diets were instituted, as much as 0.12 g N/kg/day (Case 1) and 0.14 g N/kg/day (Case 2) being retained as positive balances. Although there was a tendency for balances to become smaller as time went on, Case 1 was observed to retain 450 g N in his body over a period of 513 days, an approximately equal amount being lost in the urine. The effect of increasing calorie intakes from 35.5 calories/kg to 47 calories/kg in Case 2 was very striking, the average deposition of protein being increased from 0.08 to 0.15 g N/kg/day; in each of these periods, the protein intake was similar both in amount (0.28 g N/kg/day) and in composition (basal diet and liver residue protein). In contradistinction to Liu and Chu's subjects, these patients did not gain weight to any great extent, and it may be questioned whether even more rapid repletion of protein might not have been obtained with higher calorie intakes. The efficiencies of utilization of the protein supplements which were found (about 30 per cent) may therefore represent minimum figures. For this reason, the small differences reported between the biological efficiency of the various types of animal protein supplements may be regarded as of doubtful significance. A further point of great interest made very clearly in Keutmann and Bassett's important paper[10] is that only a small proportion of the "deposited" protein could have been represented by intravascular plasma proteins, the majority presumably having gone to rebuild depleted tissues.

The careful studies of Farr[9] were concerned exclusively with five children, and therefore strictly fall outside the present discussion. But the findings involve an important principle, and must be examined briefly. By adult standards, very high protein intakes were given, ranging from 0.19 to 0.64 g N/kg/day. During short balance periods, increasingly large positive nitrogen balances were obtained as the protein intake was raised up to the level of 0.56 g N/kg/day. With a further increase, less strongly positive balances resulted, suggesting that an optimal intake could be defined. Farr's children were maintained for most of the time on a constant calorie intake (1000

calories or between 56 and 74 calories/kg) and in spite of considerable cumulative amounts of assimilated protein (e.g., 30 g N in Case J.M.) they did not gain weight. It is well known that children require more calories than adults, and it seems likely that even more strongly positive nitrogen balances might have been obtained, especially on the higher levels of protein intake, had the diets then included more calories. We have recently studied* a boy of 23 kg, 8 years old, on a steady protein intake equivalent to 0.49 g N/kg/day. On 63 calories/kg, he retained 0.15 g N/kg/day, but when additional carbohydrate was given, the nitrogen retained rose by one-third to 0.20 g N/kg/day. The importance of calorie intake has also been stressed by Twiss.[22]

It now seems that steady increases in positive balance result from greater intakes of protein up to limits dictated only by the ability to eat more food, provided that calorie intakes are also allowed to rise. In the studies by Blainey,[12] the diets of three nephrotic patients were varied so as to contain between 0.12 and 0.84 g N/kg/day; the usual calorie intakes were between 29 and 56 calories/kg, though on occasion, extreme variations of 21 to 69 calories/kg were permitted. In general, the diets remained "balanced," so that the calorie and nitrogen intakes rose together; the usual relationship was 100 calories/g N, and always fell between 70 and 140 calories. Under these conditions it was possible to deduce regression lines relating the balances to the intakes of nitrogen. Additional protein in the diet increased the positive nitrogen balance in each of the three patients with efficiencies of 68 per cent (±21 per cent), 78 per cent (±17 per cent) and 65 per cent (±12 per cent)—the figures in parentheses being standard errors. The main protein supplements used were milk powder and calcium caseinate, the basal diet including other forms of animal protein. The minimum intake to prevent nitrogen wastage was calculated as lying between 0.1 and 0.2 g N/kg/day, in two patients. In the third, an adolescent girl, it was 0.37 g N/kg/day, though it is noteworthy that this patient was receiving the smallest number of calories per gram of nitrogen intake of all three. With the passage of time and after considerable amounts of protein had been retained, two of these patients showed a tendency to remain in less strongly positive nitrogen balance on any given diet; this could be interpreted as an increase in the minimum level of intake needed to prevent nitrogen wastage, supplements above this minimum level still being used with high efficiency. Throughout the periods of study, a considerable proteinuria persisted, equivalent to a wastage of 0.02 to 0.07 g N/kg/day, though it did not appear to be aggravated by the high levels of protein intake. In one of the patients, a considerable aminoaciduria was also found, especially marked during the periods of high nitrogen intake. In this patient, the total urinary non-protein nitrogen often exceeded the sum of urea- and ammonia-nitrogen excretion by 5 g daily, as against the usual difference of about 1 g. Thus an additional nitrogen wastage equivalent to about 0.08 g N/kg/day was imposed on this patient. Aminoaciduria is found only in a minority of nephrotic patients. It is apparently due to defective reabsorption by the renal tubules, since the concentration of amino acids in the blood is not raised. Gross aminoaciduria may present an additional reason for maintaining a high level of protein intake.

Dietary Recommendations

We may now sum up present knowledge of the dietary requirements of the adult nephrotic patient as judged by these various nitrogen balance studies. A high consumption of proteins and of calories leads to steady replenishment of wasted body tissues. This wasting may occur if protein intake falls below about 0.14–0.20 g N/kg/day, i.e., below 60 to 90 g protein in a normal-sized adult. Occasionally, wasting occurs on even higher intakes. It may also occur if the caloric intake falls below about 30 calories/kg on any protein intake. In consequence, many patients who have been ill for some months are grossly depleted when presenting for further treatment. To take a specific example, a 70-kg patient may be depleted of 490 g N, i.e., 7 g N/kg body weight.

* Unpublished observations.

Table I shows the positive balances to be expected on our experience from various levels of dietary intake, and the resultant times for restitution of the wasted tissues.

Diets similar to No. I are in fact often prescribed; they prevent further depletion, and, if proteinuria diminishes spontaneously or with drugs, may lead to adequate recovery; otherwise, disability is liable to remain prolonged, as shown in the table. Diets Nos. II and III are attainable with modern high protein supplements; the use of No. III is our current practice. Diet No. IV does not seem a practical diet unless forced feeding is used, and should perhaps be reserved for exceptional circumstances; it has not been used by us. (As already noted, if these diets are to be adapted to children on a body-weight basis they must be modified especially so as to provide a more liberal allowance of calories.)

TABLE I

Hypothetical Subject 70 Kg—Depleted of 490 Grams of Nitrogen

Diet No.	Intake/day			Expected Balance	Days for repletion
	Calories	Protein	g N/kg		
		g		g N/kg	
I	2100	96	0.22	+0.01	700
II	2500	118	0.27	+0.05	140
III	3000	152	0.35	+0.10	70
IV	3800	218	0.50	+0.20	35

DISCUSSION

The search for an optimal diet for the nephrotic patient is of great interest, and many problems remain unanswered, both of a theoretical and practical nature. On the theoretical side, these clinical findings need to be related to balance studies in normal humans, to animal experiments and to fundamental biochemical facts. Calloway and Spector[23] have brought together various human nitrogen balance studies, plotting the results against calorie intake and against nitrogen intake. These graphs, though not concerned with body repletion, provide additional justification for increasing calorie and nitrogen intakes *pari passu*. The review by Allison,[24] as part of a wider discussion, defines the minimum nitrogen requirements for zero balance to be maintained in depleted animals. This appears to be somewhat lower, weight for weight, than the minimum for nephrotic patients, who have an obligatory loss of serum proteins, mainly albumin. This represents a drain not only of nitrogen but also of essential amino acids which must be provided in the dietary protein. For example, serum albumin is rich in sulfur-containing amino acids as compared with beef muscle and milk. Grabfield[25] observed retention of sulfur together with nitrogen in the ratio of 10.5:100 during convalescence in nephrosis. In theory, if the ideal amino acid composition of food protein for further synthesis of the depleted body protein could be calculated, and provided that the losses of non-protein nitrogen in the urine could be reduced to the levels attained in starvation, the efficiency of utilization of food protein should be near to 100 per cent. This rational approach is well set out in a review by Block and Mitchell,[26] and analyses are given of the composition of various tissues. In practice, although muscle and serum proteins are obviously depleted in long-standing nephrotic states, the relative contributions of different body proteins to the overall state of depletion is not known. Fair efficiency of utilization is obtained by the use of milk supplements to a mixed diet which includes other forms of animal protein, and no advantages have been seen when dialyzed animal serum was used to replace some of the milk.

It is also tempting to speculate about the large caloric requirements of the nephrotic patient during protein repletion. Presumably, this is needed in part for the interconversion of amino acids and for subsequent synthesis of protein. It might thus depend upon the

quality of protein in the food. The caloric efficiency of protein synthesis in the human body is not accurately known; it seems that about 100 calories may be needed for each extra gram of nitrogen assimilated and retained within the body. This may be compared with the calorie value of protein when degraded (about 25 calories/g N).

Another theoretical question concerns the best form in which to supply calories—fat or carbohydrate. Our diets have usually been arranged to give carbohydrate:fat ratios of between 3:1 and 2:1, although ratios as low as 1.3:1 have been given. In practical terms, the milk determines the minimum fat content of the high protein diets which include large amounts of this form of supplement. With whole milk, protein and fat intakes are approximately equal; with skim milk and casein preparations, just over twice as much protein as fat can be given without making the diet unpalatable. As yet there is little objective evidence on which to base a choice between these alternatives for nephrotic patients. Munro[27] has compared carbohydrate and fat for assisting protein utilization in general. A few points may favor the clinical use of higher carbohydrate:fat ratios; certainly calories added in the form of carbohydrate, even ordinary cane-sugar, can be effectively used, as shown by our 8-year-old patient described above.

Although the evidence from balance studies favors the high protein, high calorie diet for nephrotic patients, two kinds of clinical question should be asked—"Are any adverse effects observed on these high-protein intakes, and can patients manage to eat such large quantities of food?" In some patients, as was shown 20 years ago,[28] some increase in the daily losses of protein in the urine may follow the institution of a high protein diet. With experience of albumin infusions, it is now well known that any rise in serum albumin concentration leads to increased proteinuria, without any alteration in the glomerular permeability to protein. There is no evidence that this damages the kidney; if, for example, the serum albumin concentration is allowed to fall again (e.g., as happens after infusions), proteinuria reverts to its previous amounts. Levels of blood urea or non-protein nitrogen also tend to rise when high protein diets are instituted; as shown by Addis,[28] this also occurs in normal persons. With the possible exception of patients with very poor renal function (for example, with creatinine clearances of less than 15 ml/min), there seems to be no valid argument for restricting protein intake. The general findings with high calorie, high protein diets are of some subjective improvement and increased well-being, and the absence of any objective signs of aggravation of the disease process. More definite clinical benefit is sometimes to be seen, and is probably most likely to occur in patients with a moderate proteinuria (on the order of 5–12 g daily) and especially among those in whom the serum albumin concentration is lower (e.g., 1–1.5 g/100 ml) than that usually found at these levels of proteinuria.[5] In these patients especially, "spontaneous" diuresis may occur after a month or more of dietary treatment.

In the preceding discussion, the patient needing refeeding has been reduced almost to the equivalent of a half-empty jug, needing only to be held under a running tap to be refilled at any required rate. In practice, the nephrotic patient often requires skillful nursing and attractive presentation of his food, particularly in the early stages of treatment. In each interval between the main meals, at least one flavored drink of salt-free milk has to be given so that sufficient protein is received. A poor appetite may improve after a few days on the diet, but vomiting and sometimes diarrhea may cause real difficulties. Fortunately, the administration of cortisone or related compound often leads to rapid loss of these symptoms. The patient's outlook improves, and a satisfactory food intake can be maintained much more easily.

SPECIAL FEATURES ENCOUNTERED WITH CORTISONE THERAPY

The effects of cortisone and related compounds on the nephrotic syndrome are so strikingly beneficial that until a more radical cure is available, large numbers of nephrotic patients will be receiving these drugs. In our experience, continuous dosage with 50–150 mg

daily usually leads to a gradual fall in urinary protein losses. This is not accompanied by any fall in serum protein concentration; indeed, a rise in the total of circulating protein ensues, and so after a variable time, diuresis follows. The serum albumin concentration then rises to a new level in equilibrium with the reduced level of proteinuria. The amounts of these changes are usually such that an improvement in protein-retaining power by the kidney can be regarded as responsible. (Increased serum protein production can occasionally be inferred in addition, but this change commonly follows improved feeding before cortisone is instituted.) The improvement in renal function is not fully understood, but appears to be due to suppression of an inflammatory or allergic condition. Its onset is accompanied by a return of serum complement to normal levels,[30] but further gradual improvement is found on steady cortisone dosage for very many months. The improved renal function may extend beyond protein retention to the disappearance of aminoaciduria and glycosuria and to substantial improvements in creatinine clearance.

In one sense, the lessened urinary losses of protein suggest that protein feeding is less important when cortisone is to be given. But depletion still needs to be remedied. This can be done, for metabolic studies by Blainey (unpublished) have shown that the administration of cortisone in moderate dosage produced no alteration in the positive state of nitrogen balance in two nephrotic patients. One of these, who remained in strongly positive balance while receiving 150 mg cortisone daily had shown, some months previously, equally marked negative nitrogen balances on 100 mg of corticotropin (ACTH) daily. This effect of ACTH is either mentioned or implicit in blood and urine nitrogen estimates by many authors, and it seems very undesirable to induce negative nitrogen balances in patients who may already be grossly depleted. It is known that larger doses of cortisone may lead to protein catabolism, and perhaps the difference observed between ACTH and cortisone in this respect was merely a dosage effect. At all events, in assessing the relative merits of cortisone, hydrocortisone, and the newer synthetic drugs of this series for treating nephrotic patients, their tendency to promote tissue catabolism should be considered in relation to their anti-inflammatory effect.

The ideal diet for a patient receiving continuous cortisone therapy has yet to be defined. To avoid undue exacerbation of edema, a "salt-free" diet is advised at the outset, and sodium restriction is best maintained until a definite reduction in proteinuria is achieved, or until edema is nearly lost, as described in an earlier section. Thereafter, severe salt restriction does not seem necessary. A high protein diet seems advisable and may help to prevent muscular wasting. When milk constitutes a major part of a very high protein diet, intakes of calcium and of phosphorus are also high. The one patient so far studied from this viewpoint was in strongly positive calcium balance during convalescence from nephrotic edema while receiving 150 mg cortisone daily (80-kg male). Thus osteoporosis seems an unlikely complication with patients on this kind of diet; it has not so far been observed, though our present experience is still very small (about 60 patient-months).

The only complications seen with this treatment to date are mild hypertension (readily counteracted by reserpine) and obesity. Obesity is illustrated in Figure 2 by the considerable increase in fat-fold thickness of all patients during the first 6–9 months of treatment. This increase appeared to start soon after the drug was given, but accelerated after the loss of edema when partial repletion of body protein had been achieved. The percentage increases in fat-fold thickness measurements were the same on the limb and trunk sites, i.e., the distribution of the extra fat was normal. Obvious fattening of the face occurred at the same time. Comparison of the body-weight and fat-fold measurements in the three patients illustrated in Figures 1 and 2 showed distinct differences. W.H., who returned to a lighter job than he had previously carried out, showed a lesser rise in weight than in fat, and some degree of muscular atrophy may be inferred. E.S., on the other hand, who showed gross muscular wasting after loss of the edema, tended to replace muscle as well

as to gain fat; this weight curve rose more steeply than the fat line. C.D. occupies an intermediate position; ignoring the period when slight edema recurred, only a slight change in the interval between weight and fat lines was evident. Up to the present time, his physical activity has been slight, as he has started office work and has not yet taken up any considerable degree of recreational exercise. All of these three patients show less tendency to put on fat after some months of cortisone treatment; this is specially evident in C.D. who has now returned in physical appearance, as well as in fat-fold thickness, to a pre-treatment state without any change in dosage of the drug. Close dietary supervision of out-patients is not possible, even with regular follow-up interviews. Nevertheless, these patients are probably still taking more than 120 g protein daily Their calorie intake has been gradually decreased, partly on our advice, and partly by disinclination for as much food as before. Much more study is required before an optimum intake can be prescribed. At present it seems that a gradual reduction in fat intake by substitution of skim milk or casein supplements for equivalent amounts of protein in the form of whole milk is likely to be most suitable.

SUMMARY

Considerable proteinuria, hypoalbuminemia, and edema are the main features of the nephrotic syndrome; other characteristic findings are described in outline.

Methods for assessing the nutritional status of a typical nephrotic patient are discussed. Subcutaneous fat is present in normal amounts, but considerable deficit of body protein can be proved by nitrogen balance studies. Protein deficits can be roughly assessed after loss of edema by clinical examination and from body weight, if height, age, and subcutaneous fat measurements are taken into account.

Restriction of dietary sodium is useful in delaying the extension of edema. Free intakes of water and other salts are advised.

Special consideration is given both to protein and to calorie consumption. After examining evidence from published balance data, high intakes (e.g., 2.0–2.5 g protein and 45–50 calories/kg/day) are found beneficial and necessary for long periods. Such diets are made practicable by inclusion of large supplements of "salt-free" milk.

Since treatment with the cortisone group of drugs is becoming widespread, the optimal diet to accompany it requires investigation. Current experience suggests that high protein, high calcium diets are still required, but that in convalescence there should be a progressive fall in calories, possibly best effected by reducing fat intake.

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Kaliopenic Nephropathy

By JEROME W. CONN, M.D.* AND ROBERT D. JOHNSON, M.D.†

THE PURPOSE of this paper is to marshal presently available evidence that chronic hypokalemia, always associated with a significant deficit of body potassium (kaliopenia), results in characteristic anatomic and functional lesions of the renal tubules. Our own interest in this fascinating lesion has been heightened by the demonstration that it exists in the newly described clinical syndrome called primary aldosteronism.[1–5] Since in the latter condition chronic hypokalemia occurs in man via a mechanism which is unique, and different from previously recognized causes of potassium depletion, demonstration of the typical pathologic and functional lesions of the renal tubules seems finally to relate the condition to lack of the potassium ion.

In 1919 Jaffe and Sternberg,[6] reporting upon a large series of cases of chronic dysentery which had come to autopsy, noted that 25 per cent showed a specific lesion of the renal tubules. They described it as a "vacuolar degeneration" with ballooning of many of the epithelial cells, particularly those of the proximal convoluted tubules. The vacuoles did not take up stains for either fat or glycogen. The glomeruli and arterioles appeared to be spared. That the tubular changes could be "due to disturbed absorption of nutritional substances from the intestinal tract" was one of the possibilities seriously considered.

Clinically, little more was heard about this interesting lesion until 1940 when Ch'in and Hu[7] described it again in autopsy material from cases of bacillary dysentery. In 1947[8] and again in 1950,[9–12] papers appeared associating these tubular changes to chronic intestinal disease, but only Perkins *et al.*[12] related the lesion to a deficiency of potassium. Since then, the relationship of "clear cell nephrosis" or "vacuolar nephropathy" to the state of potassium deficiency associated with chronic intestinal disease has gradually become appreciated.[13–16]

In the meanwhile, tubular lesions practically identical with those described above had been produced by Schrader and associates[17] in long-term experiments in rats fed a potassium-deficient diet. This was confirmed five years later by Durlacker, Darrow and Winternitz,[18] who noted, too, a significant increase in both dry and wet weights of the kidneys after rats had been on a diet deficient in potassium for four weeks. From this same laboratory[19] came the report that renal tubular lesions indistinguishable from those produced by a potassium-deficient diet are observed in rats given repeated injections of desoxycorticosterone (DOC); and that supplementary potassium chloride prevents the DOC-induced tubular vacuolar nephropathy. Although mild polyuria occurred in the rats on potassium-deficient diets (this is true in dogs, too[20]), urinary volume was increased greatly in the rats treated with DOC over long periods of time. In the latter groups the serum sodium was elevated. Thirst, therefore, may have been responsible in part, at least, for increasing total urinary volume in the DOC experiments.

Ragan *et al.*[21] induced severe polyuria and polydipsia in dogs by administration of DOC (25 mg intramuscularly daily for six weeks). The serum sodium was elevated and the "diabetes insipidus-like" symptoms were greatly accentuated by the addition of sodium to the diet. The urinary specific gravity had fallen and was found to be poorly responsive to administered pitressin. Upon cessation of DOC, polydipsia ceased quickly (as the serum

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

* Professor of Internal Medicine, Division of Endocrinology and Metabolism, and The Metabolism Research Unit.

† Instructor of Internal Medicine in the Division of Endocrinology and Metabolism.

sodium came to normal), but it required seven days for the specific gravity to return to baseline values. These workers pointed out the distinct differences between true diabetes insipidus and the syndrome induced by excessive activity of DOC. Ferrebee and coworkers[22] continued these experiments and observed that urinary potassium increased on the very first day that DOC was given; and that excessive losses of potassium in the urine continued even after the development of hypokalemia, which appeared within 10 days (DOC—25 mg intramuscularly daily).

Fig. 1. Renal biopsy specimen from a case of primary aldosteronism subsequently cured by removal of an aldosterone-secreting adrenal cortical adenoma. Note the tubular vacuolar nephropathy. The vacuoles do not contain glycogen or fat.

Primary aldosteronism, the spontaneously occurring counterpart in man of the DOC experiments referred to above, is now an established clinical entity;[1-5,23-26] and the morphologic renal tubular lesion observed in this condition[3,5] is characteristic of that found in other states of chronic hypokalemia of diverse etiology (Fig. 1).

The functional status of the kidneys in primary aldosteronism is of great interest. Apart from a much more intense polydipsia and polyuria (due in part to the accompanying hypernatremia) than is observed in potassium depletion due to other causes, the alterations of function in both situations are very similar.[14] In the original reports describing primary aldosteronism[1-3] the following points regarding renal function were emphasized: (a) the existence of great polyuria and polydipsia; (b) hyposthenuria unresponsive to pitressin; (c) impairment of tubular capacity to reabsorb water greatly out of proportion to other defects in renal function; (d) persistently alkaline urine; (e) persistently high U/P (urine/plasma) ratios for potassium in the face of severe hypokalemia.*

Much more detailed studies of renal function in three proved cases of primary aldosteronism have been reported recently by

* This is a specific effect of aldosterone upon tubular function and does not occur in other states of chronic hypokalemia. An exception to this statement is the increased clearance for potassium in renal tubular acidosis, but this situation is very different from the renal disturbance observed in primary aldosteronism.

Dustan, Corcoran, and Farrell.[27] Their findings are precisely as those listed above, but in addition, they have been able to characterize the mechanism of the hyposthenuria. It was found that the tubular capacity to reabsorb free water ($T^c H_2O$) is mildly but persistently negative in primary aldosteronism and that this is not affected by pitressin. On the other hand, $T^c H_2O$ in true diabetes insipidus is strongly negative without pitressin, but becomes *normally positive* upon administration of pitressin. It was pointed out that the defect in water reabsorption is similar to that seen in DOC-induced "diabetes insipidus" in dogs and rats, as well as to that observed in dogs made chronically hypokalemic by potassium-deficient diets.

Thus, studies in humans with primary aldosteronism show (a) the same tubular lesion morphologically that has been observed after death in people who had been depleted of potassium by chronic intestinal disease, and (b) the same histologic lesion which is seen in animals fed a diet deficient in potassium, or fed an adequate diet but given large doses of desoxycorticosterone. Essentially the same disturbances of renal function, too, are observed under these various conditions. Obviously, the common denominator is chronic deficiency of potassium.

To what extent is this renal tubular vacuolar nephropathy in man reversible both from the anatomic and functional points of view? It is somewhat disconcerting that so few studies are available in man with which one can document his answers to these questions. Nevertheless, we believe that they can be answered with reasonable assurance.

REVERSIBILITY OF THE RENAL ANATOMIC LESION IN MAN

The only study applicable to this question is that reported recently by Relman and Schwartz.[28] Renal biopsy specimens obtained from two patients severely depleted of potassium because of chronic diarrhea showed the characteristic tubular vacuolar nephropathy. Repeated biopsies obtained after partial repletion of potassium (and before significant functional improvement had occurred) showed evidence of healing of the tubular lesion. More studies of this type are needed.

REVERSIBILITY OF THE RENAL FUNCTIONAL LESION IN MAN

Carefully performed studies in normal men with induced depletion of potassium are few.[29–34] These studies, together with observations made upon (a) patients recovering from primary aldosteronism (after removal of the adrenal tumor[4,5,27]), and (b) patients being treated with potassium for chronic kaliopenia due to diarrhea,[14,28,35] make it clear that a major degree of recovery of impaired renal function can be attained in most instances. That kaliopenic nephropathy may not be completely reversible and that it may lead to progressive renal disease has been shown recently by Fourman, McCance, and Parker in experiments upon rats.[36]

From the data available to date one can state that recovery of renal function following removal of an adrenal aldosteronoma proceeds in the following temporal order:

(1) Abrupt decrease in potassium clearance.[4,5,24,27] This rapid return of efficient renal conservation of potassium indicates that the capacity of the tubules to reabsorb potassium has remained intact despite the presence of the tubular hydropic vacuolization. This is true, too, in kaliopenia due to diarrhea in which efficient renal conservation of potassium is maintained.[28] The difference in the two conditions before treatment is due, of course, to the presence in one of them of the hormonal effect on the tubule of an excessive amount of aldosterone. This must be kept in mind when one attempts to interpret the findings in such excellent studies as those of Earle and associates,[37] Wyngaarden *et al.*,[38] and Evans and Milne[39] on cases which are now regarded, in retrospect, as examples of primary aldosteronism. In fact, this has now been proved in the case reported by Evans and Milne.[39] An aldosterone-secreting adrenal cortical tumor has been removed surgically from this patient.[40]

(2) Relief of intense polyuria and polydipsia.[4] This parallels the disappearance of hypernatremia and occurs long before there is any change in concentrating ability or in pitressin

responsiveness. Thus, it appears that much of the polyuria is secondary to polydipsia.

(3) Return of the capacity to produce an acid urine.[4,27]

(4) Disappearance of proteinuria.[4,27]

(5) When initially depressed, renal plasma flow and glomerular filtration rates return to normal slowly.[27]

(6) Return of tubular capacity to reabsorb free water[27] with gradual return of the concentrating ability.[4,27]

In the nephropathy associated with diarrheal depletion of body potassium, practically complete reversal to normal of the abnormal renal functions (depressed clearances of inulin, endogenous creatinine, and *p*-aminohippurate; hyposthenuria unresponsive to pitressin; and proteinuria) can occur after the potassium deficit has been relieved.[14,28,41] Although alkalinity of the urine is not evident here as it is in primary aldosteronism, recent studies[34] indicate that under conditions of simple depletion of potassium the ability to produce a maximum concentration gradient of hydrogen ion between urine and plasma is impaired; and that this capacity is restored by administration of potassium. Many weeks may be required before normal tubular capacity to reabsorb water is restored.[14] The possibility exists that in some cases sufficient renal damage occurs in the course of a period of kaliopenia to render return of adequate function impossible.[36]

We believe that one is justified now in speaking of *kaliopenic nephropathy* as an established entity[28] with characteristic clinical and pathologic features. The functional and pathologic lesions may be completely reversible early, but it is likely that chronicity and intensity of kaliopenia are important factors with respect to the degree of functional and anatomic recovery that is possible. Why kaliopenia produces a vacuolar nephropathy in which the major morphologic lesion is found in the cells of the proximal convoluted tubules must await more information regarding such phenomena as the relationships between potassium and tubular enzymatic activities,[41–43] and the effects of hormones upon specific cells[44] in the potassium-deficient state.

Finally, it should be pointed out that degenerative vacuolar lesions of the renal tubular epithelium, similar in many respects to those seen in kaliopenic nephropathy, have been observed under other circumstances. This is not to de-emphasize the importance of kaliopenia, but to suggest that studies of the metabolism of potassium, both general and tubular, may prove fruitful in the other circumstances. The situations which produce a tubular lesion not unlike that observed in kaliopenic nephropathy are "sucrose nephrosis,"[45–48] neomycin nephropathy,[49] and diethylene glycol poisoning.[50]

SUMMARY

Kaliopenic nephropathy must be recognized as an established clinical and pathologic entity. It can be induced experimentally by diets deficient in potassium. It is reproducible by repeated administration of large doses of desoxycorticosterone and preventable when supplementary potassium is given in such desoxycorticosterone experiments.

In man, the syndrome is observed most frequently in the potassium-deficient state associated with chronic intestinal disease. It is also present in primary aldosteronism, the renal manifestations of which are analagous to DOC-induced "diabetes insipidus" in animals.

A decreased tubular capacity to reabsorb water, not influenced by administered pitressin, is the most distinctive functional abnormality encountered in kaliopenic nephropathy. While other renal functions, too, may be impaired, hyposthenuria is disproportionately severe. Histologically, the lesion is limited to tubular cells and is characterized by diffuse hydropic vacuolarization. This anatomic lesion is observed in chronic hypokalemia in man whether the latter is produced by long-standing diarrhea on the one hand, or by an aldosterone-secreting cortical tumor on the other.

In most instances both the functional and anatomic abnormalities appear to be slowly reparable after replacement of the potassium deficit. It is likely, however, that in some cases so much damage has occurred during chronic kaliopenia that functional recovery is impossible.

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Renal Function in Scurvy

By L. EALES, M.D., M.R.C.P.*
With the Technical Assistance of T. J. TURNER†

MALNUTRITION and undernutrition have far-reaching effects on the body, and it would be surprising if there were no effects on the kidneys. Studies of the pathologic appearance of the kidneys in malnourished individuals generally reveal only an atrophy of the kidney, although Davies,[1] in discussing the characteristic lesions of kwashiorkor (believed by many to be a form of protein malnutrition), states that 11 out of 20 cases showed lesions corresponding to those first described by Hennessey[2] as "proliferative glomerulitis." The most striking feature was glomerular hyalinization. Dicker *et al.*[3] found in many of the rats on a protein-deficient diet that the tubules had undergone extensive necrosis and calcification. Furthermore, in animals renal lesions have been produced by deficiency of potassium, magnesium, chlorine, choline, and linoleic acid.[4] In man the production of a severe "vacuolar nephropathy" in states of gross potassium depletion is now a generally accepted occurrence.

Whereas in hunger edema the pronounced and almost invariable presence of polyuria might be taken to indicate abnormality of renal function, it is generally agreed that a failure to concentrate the urine is due to the mobilization of edema fluid and is not indicative of a renal lesion. According to most reliable observers, the urine is free from protein, and the urinary sediment is normal. In a report on the edematous syndromes associated with chronic malnutrition as seen in the non-European community of Cape Town, the possibility of a "nutritional" renal lesion was raised, but has not been established.[5] Even in cases of extreme starvation kidney function on gross testing is remarkably normal.

Reports of the investigation of renal function by modern clearance tests are so few that Smith[6] states in his monograph that whether or not renal function is modified by prolonged undernutrition cannot be decided from available evidence. Mollison[7] found normal inulin clearances in two very emaciated people without edema. The diodone clearance was reduced in one and normal in the other. Inulin clearances of 70 and 53 ml per minute and diodone clearances of 194 and 283 ml per minute (corrected to 1.73 square meters, body surface) were found in two emaciated subjects with edema. In 11 subjects with undernutrition, all of whom had or had had edema, McCance[8] found an inulin clearance below 100 ml per minute in only one subject.

Although, generally speaking, diets which are deficient in one aspect are likely to be deficient in others, scurvy appears clinically to be a relatively "pure" form of deficiency, and this condition was selected as a starting point for an investigation into renal function in malnutrition by modern clearance tests.

Furthermore, from the work of Ralli and associates[9] it is clear that the excretion of vitamin C in the urine is determined by the plasma level, the rate of glomerular filtration, and the maximal rate of tubular reabsorption. Although it is believed that vitamin C clearance does not become zero at very low plasma levels,[10] the investigation also provided an opportunity for testing the suggestion[11] that a possible way in which vitamin C might be conserved in the scorbutic subject is by a reduction of the glomerular filtration rate.

SUBJECTS OF THE STUDY

The 14 cases studied were adult males; 12 were Bantu heavy laborers, who in many cases

* Physician, Department of Medicine, Groote Schuur Hospital and the University of Cape Town.

† Technical Assistant, Department of Medicine, Groote Schuur Hospital and the University of Cape Town.

had come to Cape Town in search of work from as far afield as Nyasaland, one was an Indian, and the other a Cape coloured male. Most of their wages were saved for transfer to their homes, and thus they all had subsisted on an inadequate diet which was severely deficient in vitamin C and consisted almost exclusively of maize meal porridge and white bread—i.e. a low protein, low fat, cereal diet.

All of these patients when first seen had severe scurvy showing the following triad: "spongy," hypertrophied bleeding gums, often with loosening of the teeth; extensive and often multiple hematomata, occurring especially in the intermuscular septa, but also subcutaneously and subperiosteally; follicular hyperkeratosis (often with perifollicular hemorrhages). With the exception of case 1, all had anemia, which was severe in 10 of the patients. There was no gross evidence of other vitamin deficiencies and all were free from complicating disease likely to affect renal function, although case 2 had a past history of malaria and a slight firm enlargement of the spleen, while case 5 had an early Parkinsonian tremor, and case 6 had x-ray evidence of old quiescent apical pulmonary tuberculosis.

From personal observation of numerous cases of scurvy, overt signs of renal disease are absent, although very rarely hematuria may be present. The blood pressure was normal in all of these cases. The specific gravity of the urine on random testing was normal. The blood urea and the serum protein concentration in all instances were within normal limits. Four patients had an elevated temperature on admission to hospital (Table I).

METHODS

Since these subjects had subsisted on a diet which was deficient not only in vitamin C, but also notably in the quality and quantity of protein consumed, it was necessary to evaluate the effects, if any, of replacing the vitamin C and, in addition, the effect of restoration of full diet. Furthermore, in view of the severe anemia present in these cases, the effects of anemia had to be considered. In a few the effects of an elevated temperature also had to be borne in mind.

On admission to the hospital the subjects were placed at rest in bed on a control diet which aimed to reproduce the diet the patient had been taking prior to admission. It was made up of crushed maize, maize meal porridge, white bread and treacle, and black tea with sugar. Salt was not restricted. This diet was estimated to provide approximately 2000 calories and 35 grams of protein per day. One hundred grams of meat (thoroughly stewed to destroy vitamin C) were added to the control diet in cases 13 and 14.

The glomerular filtration rate (G.F.R.) and effective renal plasma flow (E.R.P.F.) were determined under various conditions.

Case 1—scurvy without anemia—was studied while on the control diet and following seven days of a full diet and vitamin C therapy. In cases 2 to 5, clearances were performed at varying times both before and after transfusion and later, after the institution of vitamin C therapy and full diet. These cases were part of another investigation into the survival of transfused red cells.[12] Citrated whole blood which had been stored for 36 hours was used. (Bank blood stored for a similar period was found to contain 1.45 mg/100 ml of vitamin C.) In cases 6 to 12, after the determination of G.F.R. and E.R.P.F. in the control state and when the temperature was normal, ascorbic acid therapy was commenced, generally by the intramuscular injection of 500 mg twice daily, with no other addition to the diet. Usually seven days later the clearance tests were repeated and after a further seven days of a full ward diet (protein content ± 70 g; calories ± 2500 per day). In general, an attempt was made to repeat observations at weekly intervals, but, owing to expediency, this routine could not be adhered to in all cases, and the intervals are noted in Table I. In cases 13 and 14, boiled meat was added to the control diet, and clearances were repeated after vitamin C therapy.

The clearances were all performed in the fasting state with adequate hydration, and the technique was that of Goldring and Chasis[13] with constant plasma levels maintained with a sustaining infusion; the bladder was drained through a multi-eyed soft rubber catheter,

each period being terminated by irrigation with 50 ml of normal saline. The periods were usually of 25 minutes' duration and bloods were drawn as close as possible to the estimated midpoint of the period.

The G.F.R. was determined as the inulin clearance (in cases 1 and 2 as thiosulphate clearance) and the E.R.P.F. as the *p*-aminohippurate clearance. Renal blood flow was calculated from the renal plasma flow and the hematocrit.

The measurement of maximal tubular excretion of *p*-aminohippurate was carried out in three patients. In calculating Tm_{pah}, a value of 0.83 was used for the product FW, as recommended by Chasis and associates.[14]

Inulin was determined by the method of Roe *et al.*[15], thiosulphate by Brun's method,[16] *p*-aminohippurate by the method of Smith *et al.*;[17] and the packed cell volume by Wintrobe's method.[18]

RESULTS

All clearance determinations are the mean of two to four periods, and all figures are corrected to 1.73 square meters body surface. Table I summarizes the results in the 14 subjects, and the appropriate conditions are listed under remarks.

Renal Function during Control Period

In view of the possible effect of an elevated temperature on the clearances, attempts were made to obtain control values in the apyrexial state. This precaution was necessary. In three cases, following the subsidence of pyrexia there was a fall in G.F.R. averaging 12 ml per minute; E.R.P.F. was unchanged in two and fell in one; while E.R.B.F. fell in two and was unchanged in one. In case 11, with a moderate anemia (packed cell volume 36 per cent), and where there was no pyrexia, three control determinations at weekly intervals gave constant values for the various functions.

Excluding cases 13 and 14, who were on control diet plus boiled meat, the mean of the figures obtained during the control periods immediately before the institution of therapy and when the temperature was normal are shown in Table II (Goldring and Chasis[13] figures for normal males are given for comparison).

Glomerular Filtration Rate: The G.F.R. in some instances was well within normal limits, although in seven cases it was below 100 ml per minute, the lowest figure encountered being 74 ml per minute (the second determination in case 9 while on control diet).

Effective Renal Plasma Flow: This was materially reduced in nine of the cases while on control diet, the lowest value being 158 ml per minute.

Effective Renal Blood Flow: This was markedly reduced in all cases except the first, the lowest figure being 198 ml per minute.

Tubular Excretory Mass (pah): In cases 11 and 12, Tm_{pah} was 59 mg and 89 mg per minute, respectively.

Filtration Fraction: The mean value during the control state was 28.8 per cent; in four cases the filtration fraction exceeded 30 per cent.

Scurvy without Anemia

In case 1, the clearances, which were normal while on the control diet, rose after the administration of vitamin C and a full diet, suggesting that the effects of both vitamin C and a full diet had to be investigated apart from any possible effect of the anemia in the other cases.

Effects of Transfusion

Table III summarizes the findings in four cases. In three cases there was an increase in G.F.R., in one there was a fall. The E.R.P.F. was unchanged in two, in one it rose considerably, and in the other it fell. The E.R.B.F. increased in all except one (case 4), in which the hematocrit had fallen from its immediate post-transfusion level (a fall in the serial daily readings of the hematocrit was observed in some patients maintained on control diet).

The institution of vitamin C therapy and a full diet resulted in no significant change in G.F.R. and a notable increase in E.R.P.F. in only one of the four cases, while the E.R.B.F. increased in all. In this small sample the differences, however, between the final and control figures were not statistically significant by conventional standards. (E.R.P.F., $t = 0.986$.

TABLE I

Cases of Scurvy: Renal Function, before, during, and after Treatment

	Age	Glomerular filtration rate	Effective renal plasma flow	Filtration fraction	Packed cell volume	Effective renal blood flow	T_{mpah}	Remarks
		ml/min	*ml/min*	%	%	*ml/min*	*mg/min*	
1.	26	**128**	**587**	21.8	**48**	**1129**		On control diet
		170	912	18.7	50	1820		After vitamin C and full diet for 7 days
2.	±40	**119**	**570**	20.9	**27**	**782**		On control diet
		135	550	24.6	40	833		After transfusion of 1.4 liters of blood 7 days previously
		141	570	18.8	46	1391		After vitamin C and full diet for 5 days
3.	56	**88**	**327**	26.9	**20**	**409**		On control diet
		109	334	32.6	33	498		After transfusion of 1.8 liters of blood 6 days previously
		93	346	26.9	38	568		After vitamin C for 7 days
		95	316	30.0	44	565		After vitamin C and full diet for 16 days
4.	50	**139**	**335**	41.5	**16**	**399**		On control diet
		100	281	35.6	24	370		After transfusion of 2.4 liters of blood 7 days previously
		101	308	32.8	44	550		After vitamin C and full diet for 26 days
5.	44	**95**	**158**	60.0	**20**	**198**		On control diet
		128	344	37.2	32	505		After transfusion of 1.8 liters of blood
		137	570	24.0	36	890		After vitamin C and full diet for 18 days
6.	60	**83**	**334**	24.8	**20**	**413**		On control diet
		84	397	21.1	31	575		After vitamin C for 7 days
		99	436	22.7	41	740		After vitamin C and full diet for 8 days
		81	438	18.5	46	810		After vitamin C and full diet for 35 days
7.	50	**91**	**262**	33.8	**31**	**380**		On control diet
		87	270	32.2	33	403		After vitamin C for 7 days
		76	445	17.2	40	741		After vitamin C and full diet for 9 days
8.	30	**107**	**500**	21.4	**29**	**705**		On control diet
		137	626	25.1	31	908		After vitamin C for 7 days
		132	727	18.1	38	1171		After vitamin C and full diet for 7 days
9.	52	85	400	21.2	22	513		On control diet. (Temperature 100)
		74	**390**	18.9	**24**	**514**		On control diet—7 days later. (Temperature normal)
		76	419	18.1	28	583		After vitamin C for 7 days
		85	550	15.4	40	918		After vitamin C and full diet for 7 days
10.	25	118	366	32.3	33	547		On control diet. (Temperature 102)
		114	**367**	32.0	**27**	**504**		On control diet. (Temperature normal)
		104	477	21.8	34	708		After vitamin C for 7 days
		132	720	18.3	37	1144		After vitamin C and full diet for 7 days
		134	552	24.3	46	1022		After vitamin C and full diet for 17 days
		134	580	23.1	48	1118		After vitamin C and full diet for 38 days

TABLE I (Cont.)

	Age	Glomerular filtration rate	Effective renal plasma flow	Filtration fraction	Packed cell volume	Effective renal blood flow	Tm_{pah}	Remarks
		ml/min	*ml/min*	%	%	*ml/min*	*mg/min*	
11.	31	79	377	20.9	36	589	57	On control diet
		76	388	19.6	34	588	41	On control diet
		80	**368**	21.6	**36**	**586**	**59**	On control diet
		78	382	20.4	37.5	612	57	After vitamin C for 7 days
		75	349	20.4	43	614	52	After vitamin C for 14 days
		95	419	22.7	47.5	799	75	After vitamin C and full diet for 7 days
12.	45	99	575	17.2	23	746	92	On control diet. (Temperature 100.8)
		78	**443**	17.6	**19**	**548**	**89**	On control diet. (Temperature normal)
		80	397	20.1	32	584	83	After vitamin C for 7 days
		87	386	22.5	42	666	72	After vitamin C and full diet for 7 days
13.	52*	113	441	25.6	14	513		On control diet plus 100 g boiled meat. (Temperature up to 100)
		103	541	19.1	14	630		Control diet plus 100 g boiled meat for 7 days. (Temperature still elevated.) 6 days previously 1.0 liters of blood was transfused
		105	571	18.4	31	828		After vitamin C plus full diet for 15 days
		143	570	25.1	40	950		After vitamin C and full diet for 25 days
14.	29	125	—	—	27	—	69.1	On control diet plus 100 g of boiled meat
		108	686	15.7	41	1162		After ascorbic acid and full diet for 25 days

NOTE: Boldface figures in this table denote control figures from which Table II was compiled.

* Case 13 showed the severest degree of anemia. Vitamin C therapy and a full diet were begun immediately after the second set of clearances because of the development of further hematomas in the calves and, furthermore, the packed cell volume which had risen from 14 per cent to 19 per cent following blood transfusion had fallen steadily to 14 per cent over a period of six days. The temperature subsided six days after the start of vitamin C therapy and full diet. Recovery was uninterrupted thereafter.

TABLE II

Mean Values in 12 Scorbutic Patients during the Control Period Compared with Values for Normal Males (Goldring and Chasis[13] and Smith[6])

Subjects	P.C.V.	G.F.R.	E.R.P.F.	E.R.B.F.	Tm_{pah}
	%	*ml/min*	*ml/min*	*ml/min*	*mg/min*
Scorbutic patients	26.5	99.7 ± 20.4 (12)	396 ± 120.4 (12)	547 ± 229.4 (12)	74.0 (2)
Normal males	—	131 ± 21.5 (69)	697 ± 135.9 (69)	1209 ± 256 (61)	79.8 ± 16.7 (35)

Figures in parentheses indicate number of subjects.

P <20 per cent; E.R.B.F., t = 1.962, P <10 per cent.)

The Effect of Vitamin C Therapy, and Later Vitamin C Therapy Plus Full Diet

Vitamin C given intravenously (1000 mg) as an acute experiment in several patients had no immediate effect on the clearance values or on Tm_{pah} in case 12.

Table IV summarizes the findings in seven cases treated first with vitamin C only and later by the addition of a full diet.

TABLE III

Cases of Scurvy: Renal Function before, after Transfusion, and after Vitamin C Plus a Full Diet

Case	Glomerular filtration rate			Renal plasma flow			Packed cell volume			Renal blood flow		
	Control diet	After transfusion	After vit. C + full diet	Control diet	After transfusion	After vit. C + full diet	Control diet	After transfusion	After vit. C + full diet	Control diet	After transfusion	After vit. C + full diet
	ml/min	*ml/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*	%	%	%	*ml/min*	*ml/min*	*ml/min*
2	119	135	141	570	550	750	27	43	46	782	966	1391
3	88	109	95	327	334	316	20	35	44	409	498	565
4	139	100	101	335	281	308	16	24	44	399	370	550
5	95	128	137	158	344	570	20	32	36	198	505	890
Mean	110	118	118	348	377	483	21	33	43	447	585	849

TABLE IV

Cases of Scurvy: Renal Function before, after Vitamin C, and after Vitamin C Plus a Full Diet

Case	Glomerular filtration rate			Renal plasma flow			Packed cell volume			Renal blood flow		
	Control diet	After vit. C	After vit. C + Full diet	Control diet	After vit. C	After vit. C + full diet	Control diet	After vit. C	After vit. C + full diet	Control diet	After vit. C	After vit. C + full diet
	ml/min	*ml/min*	*ml/min*	*ml/min*	*ml/min*	*ml/min*	%	%	%	*ml/min*	*ml/min*	*ml/min*
6	83	84	99	334	397	436	20	31	41	413	575	740
7	91	87	76	262	270	445	31	33	40	380	403	741
8	107	137	132	500	626	727	29	31	38	705	908	1171
9	74	76	85	390	419	550	24	28	40	514	583	918
10	114	104	132	477	720	552	27	34	37	504	708	1144
11	80	78	95	368	382	419	36	37.5	43	586	612	799
12	78	80	87	443	397	386	19	32	42	548	584	666
Mean	89.6	92.3	101	393	459	502	25.1	32.4	40.1	521	625	883

NOTE: Duration of treatment periods was seven days except the "full diet" periods in cases 6 and 7, which were 8 and 9 days, respectively. In case 11 vitamin C was given for a further seven days after "vitamin C period" values recorded in this table (see Table V).

The G.F.R. showed a slight rise both after the administration of vitamin C alone, and after the addition of the full diet. The differences between the means were not statistically significant. The E.R.P.F. rose progressively from a mean value of 396 ml per minute to 502 ml per minute. Only the difference between the means while on control diet and after vitamin C plus a full diet was statistically significant ($t = 3.40$, $P < 1$ per cent). The E.R.B.F. increased progressively from a mean value of 521 ml per minute to 883 ml per minute, and again only the difference between the final and control values was highly significant ($t = 1.193$, $P < 0.5$ per cent). Tm_{pah} in case 11 was unchanged after 14 days of vitamin C therapy, although the hematocrit had reached 43 per cent. With the institution of a full diet a higher value was obtained—an increase of 25 mg per minute. On the other hand, in case 12, the Tm_{pah} after therapy was lower than the control value.

The overall apparent increase in glomerular filtration rate was less striking than the rise in effective renal plasma flow and renal blood flow. The fact that the mean E R.P.F. and E.R.B.F. after vitamin C therapy plus full diet were significantly different from the mean control values need not mean that the addition of a full diet is responsible for the significant difference, for in most cases the circumstances were such that vitamin C alone could be given only for seven days, by which time the mean increase in the hematocrit was 7.1 per cent. A further increase of 7.7 per cent had occurred by the time the succeeding clearances were formed. Hence vitamin C, if allowed to exert its effect for a longer period, may have produced a further change. Only in case 10 was it possible to obtain values at seven days

TABLE V

Case 11: The Lack of Effect of Vitamin C Over a Period of 14 Days Followed by an Increase in Clearances after 7 Days on a Full Diet

	G.F.R.	E.R.P.F.	P.C.V.	E.R.B.F.
	ml/min	*ml/min*	*%*	*ml/min*
Control diet	80	368	36	586
After 7 days of vitamin C	78	382	37.5	612
After 14 days of vitamin C	75	349	43	614
After 7 days of full diet in addition to vitamin C	95	419	47.5	799

and at 14 days after vitamin C therapy alone. There was no real difference between the values as illustrated (Table V) until the full diet was added to this regime.

Control Diet and Boiled Meat

The filtration rates were normal during the initial investigation in cases 13 and 14, who had boiled meat in addition to the control diet. Tm_{pah} in case 14 was within normal limits. In case 13 the temperature remained elevated and in view of the increasing severity of the anemia vitamin C therapy and a full diet had to be instituted before the temperature returned to normal.

DISCUSSION

It would appear that whereas in some cases of scurvy there is a slight reduction in glomerular filtration rate and a greater reduction in the effective renal plasma flow, the most striking feature is a reduction in the effective renal blood flow.

Effect of Age

However, in considering the overall results the additional factor of age had to be considered: Watkin and Shock[19] have found that standard inulin and PAH clearances and Tm_{pah} declined in a linear fashion from the fourth through the ninth decades. Regression equations have been computed for the various functions per 1.73 square meters body surface in 110 male subjects ranging in age from 19 to 92 years. Their subjects were selected for study on the basis of history, physical findings,

TABLE VI

Comparison of Actual Glomerular Filtration Rate Values Below 100 ml/min with Expected "Normal" Values Corrected for Age According to Watkin and Shock[19]

Case	Age	Control figures this series	Computed "normals" allowing for age
3	56	88	91.8
5	44	95	105.8
6	60	83	87.3
7	50	91	98.8
9	52	74	96.5
11	31	80	123.0
12	45	78	104.7

and urine analysis, and all were free from manifest renal disease, diastolic hypertension, or myocardial failure. All were ambulatory, co-operative, and afebrile. If the patient material resembles that of a previous series of 70 patients reported by Davies and Shock,[20] application of their findings as a yardstick for normal renal function at various ages must be accepted with some reservation, since many of their patients had active disease, e.g. pulmonary tuberculosis, bronchiectasis, etc., and cannot be considered normal. Furthermore, variations in food intake may have to be taken into account.

Many of the Bantu are uncertain as to their exact age and, in general, declared age figures, particularly in the older age groups, have to be accepted with reserve. However, in this series there appeared to be no glaring discrepancy between their stated age, their age as estimated by testing their memory of significant local events, and their physical appearance. Of the seven control filtration rates below 100 ml per minute, four occurred in subjects who were 50 years old or more, and the age factor might thus account for the low figures. When the regression equation of Watkin and Shock[19] is applied to these low figures (see Table VI), it will be seen that, in those subjects in the older age group at any rate, there is a closer approximation, but in all instances the G.F.R. found was lower than the computed G.F.R.

While accepting that age may have been a contributory cause to the low values found in

the control state, the degree of reduction in G.F.R. was such that it was unlikely to have contributed materially to the conservation of vitamin C in the scorbutic state.

Effect of Anemia

Since case 1, who was not anemic, had normal clearances, and the remainder were anemic, the possibility of anemia as a cause for the findings is to be seriously considered, especially as Bradley and Bradley[21] found in 15 patients with chronic anemia that there was a slight reduction in G.F.R. and E.R.P.F. in most patients, while the effective renal blood flow was markedly reduced—findings which resemble those obtained in this investigation during the control period except that E.R.P.F. was reduced to a greater degree. The filtration fraction did not show the same slight reduction which they found in their cases of anemia. Blegen and co-workers,[22] however, have found little change in G.F.R. and E.R.P.F. in 10 patients with anemia, but the effective renal blood flow was low in anemic patients when the hematocrit was low. In two dogs rendered anemic by repeated bleeding, Paterson[23] found that effective E.R.B.F. diminished steadily with increasing severity of anemia, but E.R.P.F. remained fairly constant until a severe degree of anemia was produced. The G.F.R. diminished *pari passu*. The Tm_{pah} did not change, unlike Bradley and Bradley's finding[21] of a reduced Tm diodrast in cases of chronic anemia. In one of the patients with scurvy and anemia, Tm_{pah} was normal and in the other slightly reduced.

With the resolution of the anemia in the scorbutic patients there was a return toward normal, the effective renal blood flow showing the most striking change. This occurred following the administration of vitamin C for the stated periods and following blood transfusion, although these procedures alone resulted in only slight improvement, which was not statistically significant by conventional standards.

The difference between the means after the addition of a full diet to vitamin C therapy and the control figures in the case of E.R.P.F. and E.R.B.F. was statistically significant. Whether the improvement is to be related solely to the continued action of vitamin C in restoring the anemic state, or whether full diet was in part responsible, cannot be decided on the available information. As mentioned previously, vitamin C adminstered intravenously had no immediate effect on the clearances, and in the only case in which vitamin C therapy alone could be carried out for a period of two weeks there was no major change in the values until a full diet was commenced.

Effect of Dietary Protein

Although Nielsen and Bang[26] have reported that on a low protein diet (26.7 g protein, 2000 calories) in eight normal women the inulin clearance decreased only 7 per cent and the diodrast clearance 2 per cent, in a further six women a high protein diet did not affect inulin and diodrast clearances.[25] Despite these observations, the effect of protein in the diet is to be seriously considered in the light of the work of Pullman *et al.*[24] They found in 20 young normal subjects that, in comparison with the values on a medium protein diet (1.0–1.4 g/kg), a low protein diet (0.1–0.4 g/kg) lowered the G.F.R., while a high protein diet (2.3–3.0 g/kg) raised the G.F.R. 9.02 and 13.1 ml per minute per 1.73 square meters, respectively. All values except the fall in effective renal plasma flow on a low protein diet were statistically significant. Brod[25] accepts unequivocally that there is a rise in filtration rate on a high protein diet and that it is connected with renal hyperemia, and stresses the importance of protein in the 24-hour rhythm of the glomerular filtration rate, which parallels the rhythm of the metabolic processes in the body. Thus it is possible that the institution of full diet with its increased protein content may have contributed in part to the improvement in renal function in these cases of scurvy.

In conclusion, it is obvious, as Blegen *et al.*[22] note, that when the hematocrit is reduced a smaller renal blood flow is needed to secure the necessary renal plasma flow required for the processes of filtration and reabsorption; hence it is not surprising that in anemia the effective renal plasma flow should be only

slightly reduced. In these cases of scurvy the findings were similar to those found in anemia, except that the relative reduction in effective renal plasma flow was greater. It is felt that the findings in scurvy are attributable mainly to the concomitant anemia, but it is probable that a deficiency in the protein content of the patient's diet may be a contributory factor.

SUMMARY

Renal function studies in 14 patients with florid scurvy are reported. The glomerular filtration rate and the effective renal plasma flow were measured by clearance techniques under various conditions in all subjects. Tm_{pah} was determined in three patients.

While on a control diet which aimed to reproduce their diet before admission and when the temperature was normal, there was a slight reduction in the filtration rate, a more evident reduction in effective renal plasma flow, and a striking reduction in the renal blood flow. The reduction in renal blood flow is related to a reduction in the hematocrit and to a lesser extent a diminution in the effective renal plasma flow. In a single patient without anemia these functions were normal. The Tm_{pah} was normal in two patients and slightly reduced in one.

While allowing for the findings in the control state in relationship to age, the magnitude of the reduction in glomerular filtration rate was such that it was unlikely to have contributed materially to the conservation of vitamin C in the scorbutic patient.

The values reverted toward normal on treatment. Although these findings may be ascribed to the effect of vitamin C in improving the associated anemia, which was present in 13 of the patients, it is probable that the increased protein of the ward diet contributed to the restoration toward normal.

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Renal Lesions in Kwashiorkor

By J. N. P. DAVIES, M.D.*

THERE IS general agreement over many of the pathologic changes seen in the disease known as kwashiorkor. The importance of the changes in the digestive glands, liver, skin, and other organs is appreciated, and there is agreement over many of the biochemical changes which are a feature of this disease.[1] There is growing evidence that a dietary deficiency of protein is a basic factor in the etiology,[2] although the play of other and quite different types of factor may also be important.[3] It has not yet been possible to show that a specific amino acid deficiency is responsible.[4] If protein deficiency is the basic etiologic factor, then it is to be presumed that there will be lesions, although not necessarily important lesions, in all the organs and tissues of the body. There is not, however, any agreement as to the existence of a renal lesion in kwashiorkor.

CLINICAL EVIDENCE OF RENAL DISEASE

The frequency and the severity of the edema in kwashiorkor has often roused suspicions of the existence of renal disease, and, in some minds, these have been confirmed by the finding in particular cases of a slight but constant albuminuria. But while there are reports of albuminuria as a frequent finding in cases of kwashiorkor in some countries, in others it is not reported or it is denied.

In Uganda, albuminuria is very common in children with kwashiorkor, but there are usually no red blood corpuscles, leukocytes, or casts in the urine. Evidence of urinary infection is rarely seen. The albuminuria is slight in amount, it does not correlate with the severity of the disease, it does not usually disappear on treatment, and it is, of course, not present in every case. Similar findings are recorded from West Africa,[5,6] from India,[7] and from South Africa.[8] In Mexico albuminuria is rarely seen, but in occasional cases it is present, sometimes with evidence of more severe renal lesions,[9] and similar findings are recorded from Guatemala.[10] de Silva[11] reported fever and albuminuria in 66 per cent of his cases in Ceylon. But, on the other hand, Gillan[12] denied its presence in his Kenya cases, and its presence in Indian children is denied by Achar[13] and by Gopalan and Ramalingaswami.[14]

Clinical observations would, therefore, appear to show that albuminuria is an inconstant feature of kwashiorkor. It may be due, not to kwashiorkor itself, but to some associated condition, for the age at which children get kwashiorkor is also the age at which, at least in the tropics, they are also coping with malaria, respiratory disease, and parasitic invasions. Not merely may albuminuria in kwashiorkor be epiphenomenal but also of little importance, were it not that even a slight drain of protein from a severely protein-depleted organism may be important.

PATHOLOGIC CHANGES IN THE KIDNEY IN KWASHIORKOR

Pathologic changes in the kidney have been little studied. The most interesting reports were those of Smith[15] in Lagos, West Africa. These were made before the importance of kwashiorkor in tropical pediatrics had been generally recognized. They were incidental to Smith's main purpose, which was to determine from post-mortem investigations the causes of child mortality in Lagos. In 500 autopsies he recognized 14 cases of what we would now term kwashiorkor, with intense fatty changes in the liver. All showed fatty changes in the convoluted tubule cells of the kidney. He considered that these findings supported the theory that poisoning by cyanogenetic glucosides might be an etiologic factor, and thus he sought in his other cases for evidence of albuminuria

From the Department of Pathology, Makerere College Medical School, Kampala, Uganda.

* Professor of Pathology.

and fatty change. Albuminuria was found in 86 per cent of 208 cases where bladder urine was available. Fat changes were present in the cells of the convoluted tubules of the kidney in 32 per cent of 350 cases, and in the liver in 58 per cent of the 500 cases. The fat was in the periphery of the lobule in 173 out of the 290 cases positive for fat; in the remainder it was centrolobular or diffuse. It is, therefore, reasonable to suppose that kwashiorkor was present, even if unsuspected, in a great many of Smith's cases.

The presence of a considerable degree of fatty change in the convoluted tubule cells of the kidney has been found a constant lesion in kwashiorkor in Uganda. It may be slight in some cases but very marked in others, with occasional evidence of cytolysis. The nuclei are often pyknotic. The glomeruli are often congested but hemorrhages have not been seen. Exactly similar changes have been recorded from Dakar by Houssiaux.[16] Such changes do not seem to have attracted much attention elsewhere. de Silva[11] records that no renal lesions are seen in his cases. But it is not certain from the various reports if some degree of fatty change in the cells of the convoluted tubules has been regarded as a lesion.

In addition, in Uganda, certain other changes in the kidneys have been noted, hyalinization of the glomeruli, sclerosis of glomeruli, and swelling of the cells lining Bowman's capsule. The significance of these changes is, however, obscure; they occur in children and adults without kwashiorkor and are probably due to unrelated conditions.[2]

It would appear then that the only changes in the kidney which might be due to kwashiorkor are fatty changes in the cells of the convoluted tubules, sometimes accompanied by congestion of the glomeruli. The significance of these changes is obscure. The renal changes of choline deficiency in weanling animals are associated with similar but much more marked lesions, and Arends and Nieweg[17] have described lesions in the kidneys of infants which they cautiously suggest may be the results of choline deficiency. There is, however, in kwashiorkor no evidence of choline deficiency, though there is clear evidence of some breakdown in the metabolism of fat. Indeed Schwartz and Dean[18] have suggested that inability to metabolize fat may be a cardinal sign of kwashiorkor. They find a large rise in the amount of fat circulating in the blood soon after treatment has begun and believe that it represents mobilization of fat. Some of this fat might come from the kidney and, by analogy with the changes in the liver, it might be postulated that some enzymic deficiency in the tubule cells is responsible for the failure of the metabolism of fat in these cells. The cause of the fat accumulation in the tubule cells remains obscure, but it does seem to be the renal lesion in kwashiorkor. The importance of this lesion in the individual case is not known, nor are its possible long-term effects on the individual. The work of Hartroft and Best[19] has shown that severe choline deficiency lesions of the kidneys of weanling animals can profoundly affect the individual in later life. Whether the kidney lesions of kwashiorkor could be severe enough to exert such effects is an open question.

EFFECTS ON RENAL FUNCTION

It is not possible to say if the presence of such a kidney lesion has any particular effect on the renal function of a patient with kwashiorkor, for little attention has been paid to renal function in this disorder. When it is, it will be difficult to distinguish between the effects of renal lesions and the effects of changes outside the kidney. Thus, the blood urea is usually low in cases of kwashiorkor in Uganda, but after treatment with a high protein diet, the blood urea will rise rapidly to levels as high as 90 mg/100 ml. These levels are not associated with any evidence of renal failure and soon revert to normal even if a high protein diet continues to be given. This effect is, therefore, probably not due to a renal lesion although it is obvious that the normal mechanism for controlling the blood urea is in abeyance. In some cases of kwashiorkor, very high levels of blood urea may be found in dying patients, again without evidence of uremia.[2] The only evidence of renal impairment so far recorded is that phenolsulfonphthalein clearance is reduced in kwashiorkor.[20] Jayasekera *et al.*[21] reported a reduction in the total nitrogen excretion and in

the excretion of creatine, but the excretion of creatinine was normal.

It is known that there are anomalies in the handling of water in patients with kwashiorkor. When edema is severe, the urine volume is low[22] and the existence of a marked oliguria was stressed by Gopalan.[23] The edema of a kwashiorkor child is lost by diuresis. The existing evidence[23,24] suggested that diuresis is inhibited by some circulating factor which, it has been very tentatively suggested, might be the pituitary antidiuretic factor. The circulating antidiuretic factor in the blood is at a high level in cases of severe kwashiorkor and falls with improvement after treatment. The cause of this is at present uncertain, but this anomaly of water handling may be more concerned with the liver rather than the kidney.

It is well known that liver function tests in kwashiorkor show that, despite the heavy infiltration of the liver with fat, there is comparatively little functional inefficiency. We might, therefore, suppose that fatty lesions in the renal tubule cells might not lead to any great reduction in their efficiency.

CONCLUSIONS

The renal lesion in kwashiorkor consists of fatty changes in the cells of the convoluted tubules. This seems, in Uganda, to be a constant finding. Other changes that have been reported are inconstant, and their importance is uncertain.

There is little evidence to suggest any marked degree of renal damage in kwashiorkor. Functional tests will probably show little deviation from the normal. Pre-renal lesions will probably prove more important than renal lesions.

ADDENDUM

Professor J. H. Heller, of the Department of Pharmacology of the University of Bristol, England, visited Uganda for a brief period to study some aspects of kwashiorkor, with the aid of the Medical Research Council of Great Britain. In the short time at his disposal he was not able to complete his full program, but he has generously allowed me to quote some of his findings which are "reasonably clear."

"(1) Plasma concentrations of sodium and potassium, in infants with pronounced edema but not with diarrhea, before and after treatment, were not significantly different, suggesting that changes in the plasma electrolyte level are not intrinsic features of kwashiorkor.

(2) Infants with untreated kwashiorkor seemed unable to concentrate or dilute their urine to the same degree as white infants of the same age group. After administration of a standard dose of water, the percentage of the water load excreted was lower than in European controls (in England).

(3) White children of an age group similar to that of the children with kwashiorkor concentrate and dilute their urine as well as adults, but do not (as adults do) excrete a volume of urine equal to that of the test dose within three hours.

(4) Small amounts of protein in the urine were found in 7 out of 16 infants. Four of these children with proteinuria were re-examined after treatment. Protein could no longer be detected in the urine.

(5) Capillary permeability tests were done on a small number of edematous and non-edematous children, but no significant difference was found.

(6) Antidiuretic activity in the plasma of blood obtained by internal jugular puncture ranged from values equivalent to less than 15 to 100 μU vasopressin per ml plasma. High values were found even when the infants were losing edema fluid under treatment."

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Observations on the Renal Defense of Body Composition in Children

By JACK METCOFF, M.D.*

THE QUANTITIES of water and the principal extracellular ions filtered at the glomerulus, and reabsorbed by the renal tubules daily, are equivalent to the passage of the total extracellular fluid through the kidneys some 14 to 15 times daily. The volume and composition of the extracellular phase in the steady state is, therefore, a function of the rate of filtration and of the effectiveness of the kidney tubules in selectively adjusting the reabsorbate to maintain normal composition. These renal activities constitute the first line of defense of the body composition.

A constant exchange of water and electrolytes across tissue cell membranes preserves the integrity of functioning protoplasm. Marked variations in extracellular fluids will impose modifications in the nature and rate of cellular transport and metabolism. This provides a second line of defense of body composition.

When the kidneys are diseased or when some extrarenal disturbance requires an adjustment beyond their maximal compensating capacities, the quantity and composition of the reabsorbate are changed and the composition of extracellular fluid becomes distorted. Since nephrons usually are afflicted to varying extents, particularly during disease states, the structure of the body fluids will be the resultant of a balance struck between the inadequacies of some nephrons and the compensations of others on the one hand, and the net activities of tissue cells with regard to transport of water and ions on the other.

It is the purpose of this report to examine a few instances where these interrelationships are at least partially clarified. Alterations in discrete renal functions, renal conservation of water and transport of selected ions, and simultaneous changes occurring in the composition of tissue will be described in immature and growing infants, and in children suffering from chronic malnutrition and certain primary cellular and renal disorders.

IMMATURITY

Renal functions are thought to be reduced in normal infants, but with maturation of these functions to levels equivalent to adult values as the child grows older.[1–3] McCance[4] recently suggested that the understanding of juvenile renal function had been delayed by the use of surface area as an incorrect basis of comparison. Since the primary purpose of renal function is to regulate the constancy of the body fluids, he suggested that renal clearances might be compared more accurately on the basis of the total body water which they governed than upon that of surface area. In the infant, this area is large in relation to his small body mass. Table I is modified from McCance's re-evaluation.[4] Discrete functions of the infant's kidney seem approximately equivalent to those of the adult when total body water is used as the standard of reference.

The premature or newborn infant is unable to elaborate a urine more concentrated than about 800 mosm/l (Fig. 1),[5,6] while the concentrating mechanisms of the thirsting adult permit excretion of a urine containing about 1400 mosm/l of solute.[7] Renal excretion of water is known to be influenced by (1) the

From the Department of Pediatrics, Harvard Medical School and the Children's Medical Center, Boston, Massachusetts.

* Present address: Department of Pediatrics, Michael Reese Hospital, Chicago, Illinois.

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TABLE I

Glomerular Filtration Rates (Inulin) after McCance[4]

Age of children	No. of children	Reference	Per sq meter surface area	Per liter body water
days			*ml/min*	*ml/min*
2–8	4	1	20	2.0
3–13	7	2	28	2.6
2–22	11	3	28	2.9
8–28	4	2	29	2.8
54–118	9	3	39	3.5
138–365	12	3	58	4.9
Adults	—	—	69	2.9

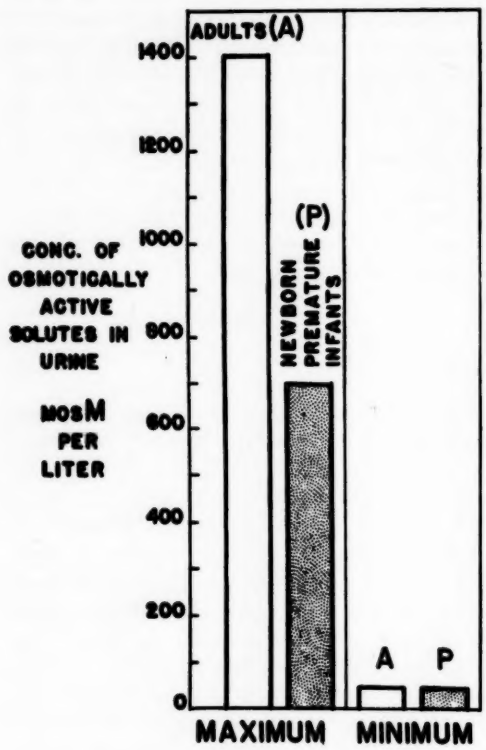


Figure 1

(Taken from Barnett and Vesterdal.[5])

level of glomerular filtration, i.e., the load of water presenting for excretion per unit time; (2) the solute load in the tubules obligating delivery of an approximately isosmotic quantity of water to the distal tubule, where the final composition of the urine is achieved; and (3) the quantity of circulating antidiuretic hormone acting upon the distal tubules to yield a reabsorbate containing osmotically free water and leaving in the urine that concentrated solute claiming removal. Although the precise mechanism regulating these activities has not been established, it is clear that when any one of these three factors is varied, the final composition of the urine will be modified.

As pointed out by Barnett and Vesterdal,[5] the ability to excrete a maximally concentrated urine may be limited by the lower glomerular filtration rate (GFR) and tubular solute load of the very young infant as compared to the adult. In addition, the very young infant has an increased content of body water relative to body solids,[8] with apparent overhydration of the extracellular phase and reduced potassium content of the intracellular phase of the tissue.[9] Moreover, the infant, in contrast to the adult, subsists on a unique fluid intake which, although varied with advancing age, generally provides a solute load which is small compared to the water of solution. It is possible that the reduced urine volume and concentration reflects the low GFR and solute intake of the neonate. Limitation of urine solute concentration would eventually favor removal of excess water, with improved solute concentration of the body fluids. The quantity of urinary solutes requiring excretion represents the total solute intake minus those solutes retained for growth or repair of abnormal losses, plus the extrarenal losses occasioned by excretion through the skin or gastrointestinal tract.

The minimal renal water requirement of the infant for removal of solutes claiming excretion has been calculated by Pratt and associates.[10] Figure 2 is taken from their paper. In this figure the quantity of solutes appearing in the urine per kilogram of body weight per day is related to the volume and the maximal urine concentration which can be achieved on various diets. For example, the young infant ingesting a cow's milk and water mixture with added carbohydrate would present for excretion about 30 mosm/kg/day. At a maximal urine concentration of 1.4 mosm/l attained by an older infant, the minimal renal water requirement would approximate 25 ml/kg/day. For a very young infant, or one undergoing maximal conservation of solute, inability to concen-

trate the urine above about 600–800 mosm/l would increase the minimal renal water requirement to 40–50 ml/kg/day. It follows that reduction of solute load at any given concentrating capacity of the kidney will result in conservation of body water by reducing the minimal renal water expenditure. On the other hand, as concentrating capacity decreases, the minimal renal water requirement is increased with increasing solute loads. When water intake is excessive, the capacity to achieve minimal urine solute concentration having a "floor"

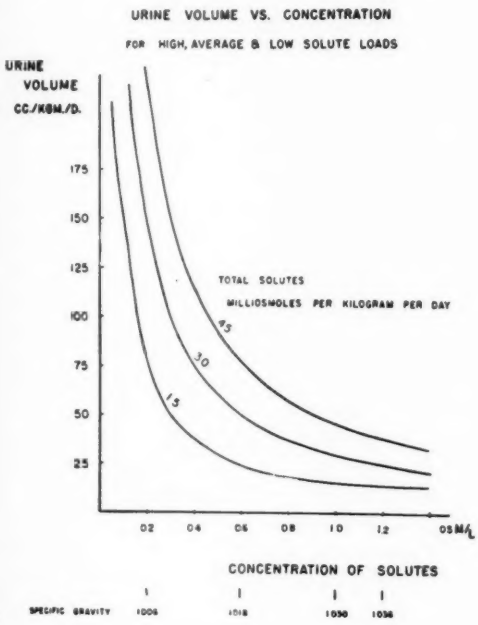


Figure 2
(Taken from Pratt, Bienvenu and Whyte.[10])

around 50 mosm/l permits removal of 300–400 ml/kg of water daily. Thus the capacities of the "immature" kidney to remove water and solute, although limiting, still provide a margin of safety large enough to cope with the quantities of water contained in the usual infant feeding mixtures.

Maintaining the concentration of the principal cations of the extracellular and intracellular fluids (sodium and potassium, respectively) is a constant task achieved with admirable efficiency by the "immature" kidney, as evidenced by normal concentrations of these ions in the body fluids of the neonate and older infant. Slight deviations in the accuracy of reabsorbate concentration would be manifest by serious changes in body composition. For example: in a 6-kg infant whose GFR was 2.0 ml/min/l body water (Table I), a consistent 2 per cent variation of sodium concentration in the tubular reabsorbate would result in a 5 to 6 per cent change in sodium concentration of the extracellular fluid ($[Na]_{ECW}$) in one day:

Total body water = 6 kg × 0.7 = 4.2 l.
GFR = 2 ml/min/l body water.
GFR/24 hours = 2 ml/min × 1440 min × 4.2 l = 12 l/24 hours.
If $[Na]_{ECW}$ = 140 mM/l and net water balance is maintained but with a consistent 2 per cent variation of [Na] in the tubular reabsorbate (ignoring urine volume),
then 0.02 × 140 mM/l × 12 l = 33.6 mM change in Na content of total reabsorbate in 24 hours.
and $\frac{33.6}{4.2 \times 140} \times 100 = 5.7$ per cent variation in sodium concentration of the extracellular fluid after 24 hours.

The ratio of Na/Cl in the tubular reabsorbate also must remain almost identical to that in the extracellular water if acid-base balance is to be preserved, since even a 1 to 2 per cent uncompensated variation in one component alone would lead to changes in the "buffer base" equivalents[11] and attendant disturbance of the $[HCO_3^-]:[H_2CO_3]$ ratio, largely from change in the $[HCO_3^-]$. If sodium were reabsorbed proportionately in excess of chloride, alkalosis would occur. If sodium reabsorption were diminished relative to chloride, acidosis would follow. Preservation of this reabsorption ratio for the principal ions of the extracellular fluids also depends upon the efficiency with which the renal tubular cell can substitute other cations, such as NH_4^+, H^+, and K^+ for Na^+ in the tubular lumen. Thus the net conservation of sodium results in acidification of the urine.[12]

The capacity of the premature infant to conserve sodium by excretion of NH_4^+ following

an NH_4Cl load is limited.[13] The slight acidosis of the premature or very young infant (CO_2 content = 20 mM/l) cannot be attributed to inadequate renal function, since bicarbonate concentration of the tubular reabsorbate is well maintained.[14] Tudvad and associates[14] also showed that an infusion of carbonic anhydrase inhibitor would block H^+ excretion by the "immature" kidney, which suggests that this enzyme system is present and normally active. They further demonstrated that the functionally "immature" kidney could remove excessive potassium (from infusion) by excretion in the urine at levels greater than simultaneously filtered, indicating a capacity for active tubular secretion of this ion, as in the older child or adult. In older infants, oral loads of sodium or potassium (N = 10 mM/kg/day) were rather slowly but effectively handled by the kidneys with excellent defense of body composition.[15]

Total body water is markedly increased relative to tissue solids in the newborn infant.[8] This increased body water is largely dependent upon expansion of the extracellular phase as deduced from balance studies,[6] dilution measurements,[8] and direct analyses of various organ systems.[16] A recent description of muscle composition of the neonate also indicates that an accumulation of sodium and relative deficiency of potassium characterizes this period[9] (Table II). With the diuresis which commonly occurs during the first postnatal week,[6] removal of a slightly hypertonic urine which contains the predominantly extracellular ions, sodium and chloride, might be expected to cause a temporary reduction of solute concentration in the extracellular fluids. Re-distribution of water from outside to inside of the cell would follow according to osmotic requirements. The resultant reduction of intracellular solute concentration, if such occurs, might impair those enzymatic activities dependent upon specific substrate concentrations of sodium and potassium. Critical levels of these ions necessary for enzyme activation or inhibition in protoplasm are not known. Reduced cell solute concentration may persist for several postnatal months, as suggested by the sum of intracellular sodium plus potassium concentrations (Table II). Obviously, the concentration of osmotically active solute within the cell cannot be defined until the states of the anionic components, and the extent to which they form complexes with cations and other molecules, are known.

TABLE II

Distribution of Water and Electrolytes in Muscle

Age	Number of children	[Ecw]*			Muscle/100g dry fat-free solids (DFFS)								
		Na	K	Cl	H_2O	Na	K	Cl	Ecw†	Icw†	[Na]i	[K]i	[Na + K]i
		mM/l	*mM/l*	*mM/l*	*Ml*	*mM*	*mM*	*mM*	*ml*	*ml*	*mM/l*	*mM/l*	
2–4 days	5	141.3	4.1	109.5	456	36.0	33.1	24.1	215	208	34.8	141.8	176.6
1–4 mo	5	134.5	4.9	122.3	392	23.4	38.1	16.7	140	252	17.6	148.9	166.5
$1^3/_{12}$–$3^6/_{12}$ yrs	10‡	141.3	4.4	114.7	360	23.4	36.2	15.3	135	225	19.1	158.9	178.0

* Serum values corrected for Donnan factor and H_2O content; F (+) = 1.02; f (−) = 1.12.

† Ecw—extracellular water; Icw—intracellular water; [ ]$_i$—concentration in intracellular water.

‡ Six serum values only.

Renal defense of cell function is suggested by the tendency to conserve solute relative to water. Presumably, renal tubular cells and the hormonal mechanisms which partially regulate them, are oriented to the gradual removal of excess extracellular solute and water. All features of this phenomenon require further study and elucidation. The capacity to handle potassium in mature fashion is present even in the premature infant, as noted above. Perhaps the paradoxical response of young infants to the injection of adrenocorticotrophic hormone (ACTH)—which causes potassium reabsorption and sodium excretion in infants, in contrast to the usual response of older children or adults—is consistent with the defensive orientation of kidney cells.

The diminished excretion of nitrogen, sodium, potassium, and chloride in the first months of life, supports the rapid apposition of tissue (i.e., growth) characteristic of this period.

In view of the relatively expanded extra-

cellular volume, altered concentrations of intracellular components, and the orientation of the kidneys to achieve a more mature and eventually constant body composition, it seems obvious that sudden disturbances of this continuously readjusting equilibrium would produce serious disorders of fluid balance. Moreover, since the infant has a large daily intake and output of water, equivalent to approximately one-quarter of his total body water, reduction of intake with increased extrarenal water losses, characteristic of diarrhea and high fevers or serious respiratory infections, rapidly bring the infant to the limits of survival. In the older child or adult, daily water "turnover" is equivalent to about one-eighth of the total body water. Thus the infant is in twice as precarious a position and survival in the absence of water intake is halved to approximately five instead of ten days for the older subject.[7] Recognition of this feature of infancy clearly demonstrated that the infant was not simply a miniature adult, and provided considerable impetus for pediatricians to acquire some familiarity with the problems of salt and water balance.

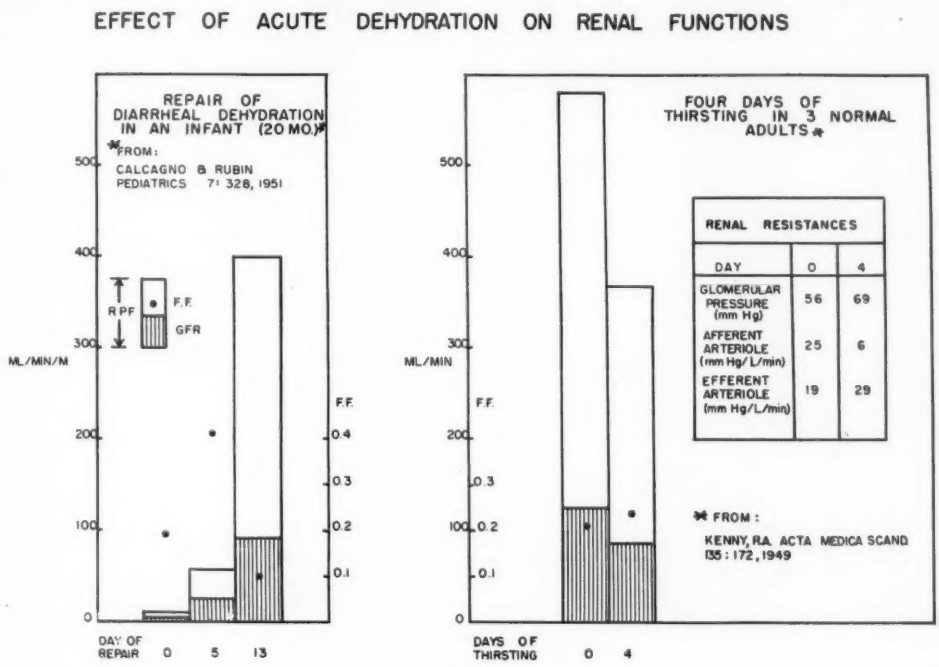

EFFECT OF ACUTE DEHYDRATION ON RENAL FUNCTIONS
REPAIR OF DIARRHEAL DEHYDRATION IN AN INFANT (20 MO.)*
*FROM: CALCAGNO & RUBIN PEDIATRICS 7: 328, 1951
ML./MIN/M
RPF
F.F.
GFR
DAY OF REPAIR 0 5 13
FOUR DAYS OF THIRSTING IN 3 NORMAL ADULTS*
ML./MIN
DAYS OF THIRSTING 0 4
RENAL RESISTANCES
DAY 0 4
GLOMERULAR PRESSURE (mm Hg) 56 69
AFFERENT ARTERIOLE (mm Hg/L/min) 25 6
EFFERENT ARTERIOLE (mm Hg/L/min) 19 29
* FROM: KENNY, R.A. ACTA MEDICA SCAND 135: 172, 1949

Figure 3

SEVERE CHRONIC MALNUTRITION IN CHILDREN

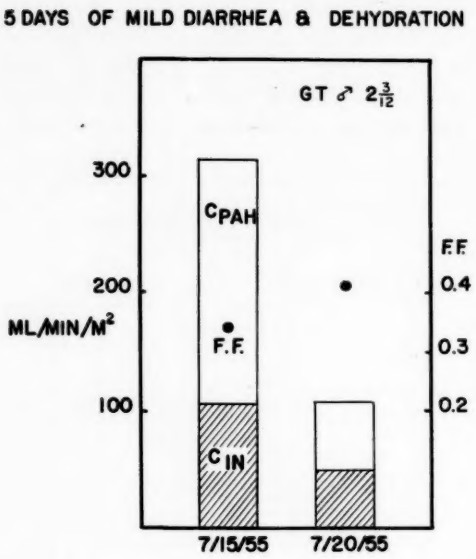
Perhaps the most common cause of abnormal body composition is chronic malnutrition. This is one of the major pediatric problems in the world and variations are described under a variety of names, including marasmus, atrophy, athrepsia, Melnahrschaden, kwashiorkor, etc.

With characteristic episodes of intercurrent infections and bouts of diarrhea causing disturbances in electrolyte and water balance, the mortality from chronic malnutrition may approach 30 to 50 per cent. Studies of tissue composition in such children have shown alterations in both extracellular and intracellular fluids. The major lesion appears to be overexpansion of the intracellular water phase. The intracellular potassium concentration is reduced, largely as a result of dilution, although the cell potassium content may also be lowered.[28] Hypotonicity of the extracellular fluid (and presumably of the total body fluid) is an im-

portant additional feature of this type of chronic malnutrition first noted by Salge,[17] and recently described in detail in Mexican children.[18]

In normal adults, dehydration resulting from a protracted limitation of water intake causes a temporary reduction in renal functions[19] (Fig. 3). Clearances, however, return to normal with rehydration. In previously well-nourished children, acute gastrointestinal disturbances may rapidly lead to severe dehydration, with a striking reduction of glomerular filtration and renal plasma flow.[20,21] The reduced clearances are associated with maximal conservation of solute characterized by excretion of a minimal volume of highly concentrated urine. The reduction in clearance usually does not imply morphologic renal damage and is rapidly reversible.[21]

In severe chronic malnutrition renal functions also are reduced.[22] Even in those



RENAL FUNCTIONS DURING CHRONIC MALNUTRITION

MEXICAN CHILDREN

	WELL NOURISHED	CHRONIC MALNUTRITION
NO. SUBJECTS	18	11
C IN (ML/MIN/M²)	63 ± 11	36
C PAH "	303 ± 70	180 *
T M PAH (MG/MIN/M²)	57 ± 14	—
F F	0.22 ± 0.05	0.32*

*7 PATIENTS

Figure 4

TABLE III

Relationship Between Circulation and Kidney Function in Infantile Dehydration and Malnutrition*
(From Kerpel-Fronius *et al.*[25])

Status and No. of children	Cardiac output	O_2 consumption	Cardiac output per 100 ml O_2 consumption	Sinus O_2 saturation	Systolic blood pressure	Non-protein nitrogen	C_{IN}†	C_{PAH}	FF
	l/M²	*ml/M²*	*l/100 ml.*	%	*mm Hg*	*mg/100 ml*	*ml/min/M²*		
5 normal infants, avg. = 3.6 mo.	2.22	140	1.54	50	80	22	39	174	0.23
7 acutely dehydrated infants (diarrhea)	1.24	136	0.90	27	65	79	10	29	0.21–0.61
9 "athreptic" infants	0.92	86	1.08	36	45	47	13	56	0.20–0.44
8 "atrophic" infants	1.45	105	1.40	43	64	27	36	159	0.24

* Averaged values from Tables I–IV in Ref. 25; 5 clearance values in second group; 6 in third.
† C_{IN}—inulin clearance; C_{PAH}—para-aminohippurate clearance; FF—filtration fraction.

instances where normal clearances are found, intercurrent diarrhea with mild dehydration causes depression of clearance, particularly if the child is hypotonic. An example of this phenomenon is shown in Figure 4. The data were obtained by Gordillo and associates[23] in a malnourished infant whose total solute concentration in extracellular fluid (serum) remained very low during the entire period of observation (266 to 269 mosm/l). During such episodes of superimposed dehydration in chronically malnourished children, azotemia was noted long ago[24] and ascribed to a functional renal insufficiency from anhydremic circulatory disturbance[24,25] (Table III). The elevated filtration fraction which may be noted in Figure 4 is consistent with this hypothesis.

Detailed information about kidney function in children during malnutrition is scarce. Perhaps the most complete study is that by Kerpel-Fronius and associates.[25] In the adult the most commonly described features are polyuria with hyposthenuria, as reviewed in detail by McCance.[26] At the Belsen concentration camp, Mollison found a significant reduction in inulin and diodone clearances in two of five malnourished adults.[27] Recent studies[18] have shown that the chronically malnourished child is hypotonic, with serum osmolalities ranging between 258 to 272 mosm/l in malnutrition without dehydration, and from 242 to 258 mosm/l in malnutrition associated with severe dehydration. These values may be compared with those of "normal" control children from the same hospital population whose serum osmolalities ranged between 287 and 296 mosm/l. Figure 5 illustrates the difference between these groups. It also shows that the range of osmolar urine: plasma (U/P) ratios determined in malnourished children usually were less than 1.0, indicating that the excreted urine was hypotonic, often despite severe dehydration.

Hypotonicity is not invariably found. It is less striking in the wasted, atrophic, nondehydrated infant. In malnourished children during episodes of superimposed acute dehydration there was simultaneous hypotonicity, elaboration of a dilute urine, and demonstration of extracellular hypotonicity, with alterations in composition of extracellular and intracellular fluids.[28] This led to the assumption that renal adjustments for conservation of water and of solute were ineffective, and that

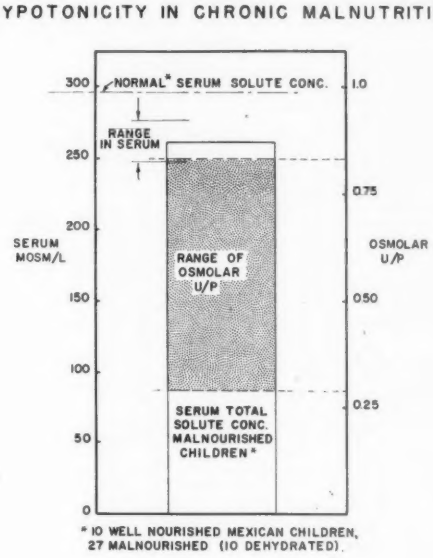


Figure 5
(Taken from Metcoff *et al.*[34])

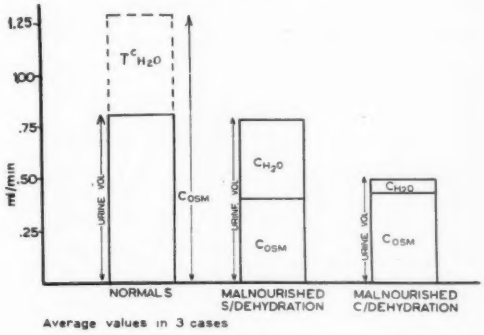


Figure 6
(Taken from Gordillo *et al.*[22])

defense of body composition was occurring in some unusual way. In the Mexican study, osmolar and free water clearances were measured in control subjects and in malnourished children, with and without dehydration.

Figure 6 from the report by Gordillo *et al.*[22] illustrates the differences existing between the three groups of children. It is based upon

measurements of three clearance periods in each of three children prior to administration of any therapy. It will be noted that the "normal" children had net free water reabsorption which averaged about 0.6 ml/min, or approximately 1 to 2 per cent of glomerular filtrate. In the nondehydrated malnourished children, free water clearance also averaged about 0.6 ml/min, or 1.5 to 2 per cent of the filtrate. With superimposed dehydration the clearance of water not obligated by solute averaged 8–9 per cent of the filtrate in chronically malnourished infants. The osmolar clearance was reduced in both groups of malnourished children as a result of the lowered filtration rate and solute concentrations of the extracellular fluid. The excretion of a copious dilute urine during dehydration and malnutrition, of which 8 to 9 per cent represented osmotically free water, suggested some defect in the antidiuretic mechanism. However, increased quantities of circulating antidiuretic hormone have been demonstrated by Heller[29] in kwashiorkor (chronic infantile malnutrition). On the other hand, infusion of pitressin in the malnourished Mexican children caused diminished urine volume with concentration of the urine in an entirely normal fashion.[28] As first demonstrated by Gilman and Goodman,[30] stimulation of endogenous antidiuretic activity can be induced by the infusion of a hypertonic solute. In Figure 7 a comparison is made of the reponse of an infant to an infusion of 0.15 M sodium chloride, as contrasted with that following administration of 0.92 M sodium chloride to another equally dehydrated malnourished infant. In both instances the initial solute concentration in the extracellular fluid was markedly reduced. Free water clearance was observed in both infants prior to the infusion. This was not significantly altered by infusion of the slightly hypertonic saline, and during this interval the urine volume was approximately equivalent to the volume of infusate administered. With infusion of a strikingly hypertonic solution, free water clearance promptly disappeared, and the urine became concentrated with a net reabsorption of osmotically free water. The concentration of total solutes in the extracellular fluid increased only 4 per cent, however, despite the administration and virtually complete retention of 90 mM of sodium chloride over a 154-minute period. The rather small increment of extracellular fluid solute concentration following retention of the large load

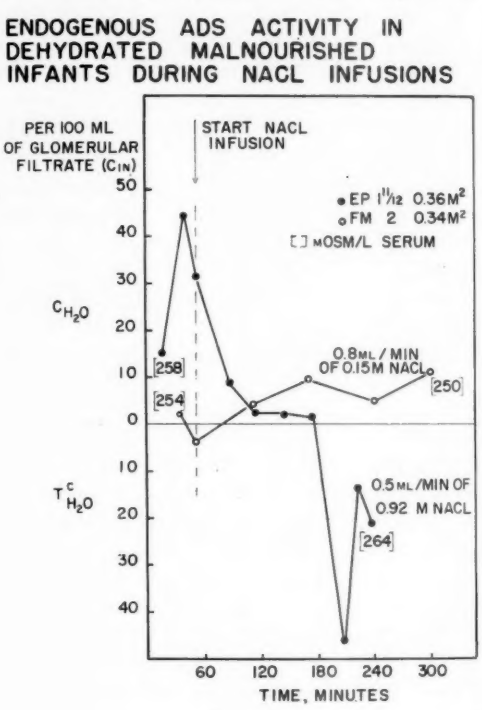


Figure 7

resulted from a redistribution of body water with expansion of the extracellular phase.

The osmolar clearance defines the proportion of the filtrate water obligated by solute requiring excretion and is expressed as $C_{osm} = \frac{U_{osm}V}{P_{osm}}$*. The free water clearance, C_{H_2O}, represents that quantity of the filtrate which is not obligated by solute. It is derived from the difference between urine volume and C_{osm}, when the V term is greater than C_{osm}. When C_{osm} is greater than the observed urine volume (V), reabsorption of some water devoid of solute

* C_{OSM} = osmolar clearance; U_{OSM} V = total urine solute excretion in mosm/min; P_{OSM} = plasma osmolality in mosm/ml.

must occur, and this is called the free water reabsorbate or $T^c_{H_2O}$.[31] The significance of these measurements and their interpretation is clearly described elsewhere.[32]

The prompt increase of osmolar clearance and conversion of tubular activity to reabsorption of water in excess of that obligated by solute during the infusion of hypertonic saline seems to indicate that the renal potential for maximum antidiuretic activity, as well as the capacity of the hypothalamic-hypophyseal system to react to appropriate stimuli, are both preserved. Thus, excretion of an osmotically dilute urine in dehydrated, malnourished children appears to represent a temporary suspension rather than an impairment of the concentrating operation. A correlation between progressively increased excretion of filtered water and reduced filtration rate was noted. It was suggested that as removal of solute-free urine serves to defend solute concentration in the body water, so progressive reduction in glomerular filtration rate might be interpreted as an effective homeostatic renal response for the conservation of the volume of body water, where reduced solute concentration and reduced filtration were previously imposed by malnutrition.[22,34]

Chronic dehydration apparently exerts less influence on tubular mechanisms to conserve water than does reduced solute concentration of the body fluids on those tubular mechanisms involved in removing water. Defense of concentration seems to have priority over defense of volume.[33] The effective defense of body water is precariously achieved during severe chronic malnutrition at a point where renal insufficiency is imminent. The marked narrowing of the range of safety within which normal flexibility of renal adjustment usually operates may account for the rapidity and ease with which intercurrent events can induce acute renal insufficiency in the malnourished child.

There are a few observations on the conservation or excretion of electrolytes during chronic malnutrition. During periods of chronic diarrhea in seven malnourished, hypotonic children, renal conservation of sodium was striking, that of potassium was less effective despite reduced intracellular potassium concentration, and chloride, like water, was excreted in abundance[34] (Table IV). The mechanism of urinary sodium retention in these children is not known. It appears to be an obvious response to the hypotonicity and hyponatremia of the extracellular fluids and conceivably might result from hormonal influences such as elaboration of aldosterone.[35] Aldosterone activity also could predispose to renal potassium loss in addition to that requiring removal after being liberated by cell catabolism, despite episodic depletion of potassium via recurrent bouts of diarrhea.

TABLE IV

Composition of Urine During Hypotonicity, Chronic Malnutrition, and Intercurrent Diarrhea*

Number patients	24-hour periods (avg./patient)	Excretion, per kg/24 hrs			
		H_2O	Na	K	Cl
		ml	*mM*	*mM*	*mM*
7	5–6	49.5	0.3	0.8	1.6
		per 1000 ml	7	17	33

* Taken from Reference 34.

A tentative hypothesis relating the changes in tissue composition and renal functions in severe chronic malnutrition has been discussed elsewhere.[34] In general, the following pattern of response was suggested: Reduction of body solids at a more rapid rate than reduction of body water results in a relative increase of extracellular volume. Hypotonicity of the body fluids then is occasioned by a loss of solute following intercurrent bouts of diarrhea and vomiting and insufficient intake of sodium and potassium relative to water. Slight overhydration of both extracellular and intracellular phases follows, a situation analogous to that observed in the newborn infant. Tissue anabolism is limited by the poor diet. Infection and diarrhea cause caloric losses and heightened energy demands which are partially satisfied by the channeling of fat and protein metabolism. Plasma proteins become depleted and cell catabolism occurs. Cellular breakdown yields, among other things, water which augments that ingested, and the water ingested plus this endogenous water increase hypotonicity. The kidneys excrete a relatively large quantity of this excess water as copious, dilute urine.

The physiologic situation becomes analogous to that occurring in continuously water-loaded individuals.[36] Maximal conservation of solute suggests that kidney tubule cells are functioning as effectively as possible. The urinary excretion of potassium liberated from cell catabolism is another indication of efficient tubule function. Reduction of glomerular filtration rate presumably represents a physiologic defense of fluid volume by limiting the rate of removal of dilute extracellular fluid by tubular operations leading to excretion of copious dilute urine. These renal adjustments cannot be overextended, and thus the flexibility of the kidneys is reduced. Continued extrarenal losses of solute and water pose a further challenge and lead to increased cellular overhydration. The excessive accumulation of water within the cell might reduce the effective substrate concentration for those potassium-activated enzyme systems which yield energy required for active transport of sodium out of the cell. Sodium then accumulates, predisposing to extrusion of potassium. This ultimately leads to inhibition of sodium-inactivated enzyme systems which in turn brings about a further reduction of cell functions to levels incapable of supporting life.

Repair of cellular concentrations, by removing excess water from the cells, may be of therapeutic importance, since both cell function and renal function may be restored by infusion of a hypertonic solution, as previously described.[34]

A PRIMARY CELLULAR DISORDER

The Lignac-Fanconi syndrome,[37] or cystine-storage disease, is thought to be a congenital or hereditary defect in the cellular metabolism of cystine. It is pertinent to this discussion because children afflicted with this very rare disorder fail to grow properly, have marked polyuria, and usually have changes in tissue composition and renal functions characterized by striking hypokalemia, hypotonicity, and reduction in glomerular filtration and renal plasma flow where these have been measured (Table V). Although biopsies have shown superimposed pyelonephritis, this is not considered to be the cause of the reduced renal function and excessive excretion of potassium. The ability of the kidneys to conserve potassium during periods of intercurrent acute infec-

TABLE V

Renal Function—Cystine-Storage Disease

Patient	GFR (C_{IN})	C_{PAH}	Urine volume	S. A.*	Serum			
					Na	K	Cl	mosm/l
	ml/min/m²	*ml/min/m²*	*ml/min*	*M²*	*mM/l*			
A. M.†	40	1.67	0.76	0.56	132.0	2.6	80	260
E. B.	13	35	0.93	0.52	128.5	1.9	90	263

* S. A.—surface area.

† A. M. $Tm_{(PAH)}$ = 13 mg/min/M².

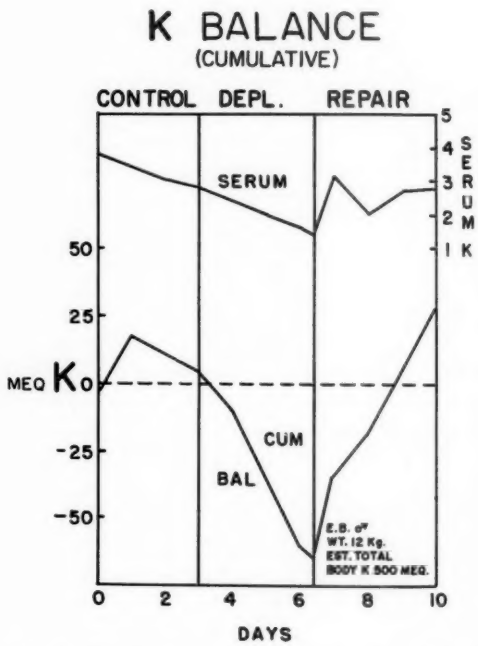


Fig. 8. Effect of dietary potassium depletion on potassium balance in child with cystine-storage disease.

tions or during potassium restriction may be limited, and striking depletion of the body stores of this cation may be induced readily (Fig. 8). In the study illustrated,[38] about 10 per cent of the estimated body potassium was removed in two and a half days of dietary potassium restriction. Extracellular fluid composition was not defended and symptomatic

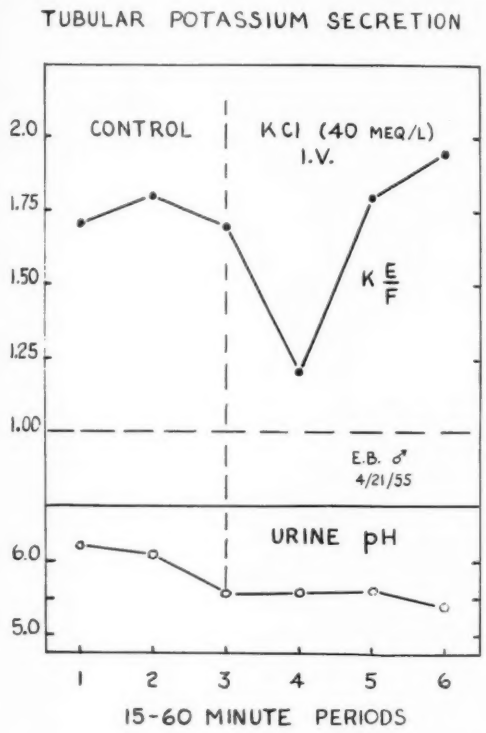


Fig. 9. Renal tubular potassium secretion in child with cystine-storage disease.

hypokalemia occurred. Repair was achieved by administering a very large oral intake of potassium. The renal cell defect was clearly evidenced by tubular excretion of potassium in amounts greater than were simultaneously filtered during control periods preceding infusion of a KCl solution (Fig. 9). It will be noted that the urine remained acid during the periods of potassium secretion, suggesting some alteration in the competitive transport scheme of H^+, K^+, and Na^+.

In another child with this same syndrome, hypokalemia was not a prominent feature. The ability to conserve potassium by removal of sodium and hydrogen ions was demonstrated by infusion of a carbonic anhydrase inhibitor combined with a nonreabsorbable anion, sodium para-aminohippurate (Fig. 10). The response was similar to that observed in control subjects.

The difference in the renal capacity of these two children with the same cellular disorder

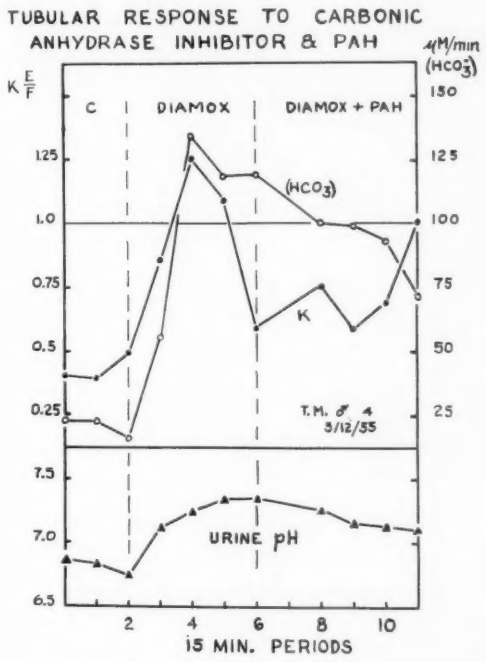


Fig. 10. Effect of Diamox® (carbon anhydrase inhibitor) and PAH loading on renal tubular potassium secretion in cystine-storage disease.

to conserve potassium suggested that sufficient disorganization of cell structure had occurred in patient EB (Fig. 9) to prevent effective renal defense of the body fluids; this was not yet the case in patient TM (Fig. 10) although the clinical status of both children was similar.

Table VI tends to support this hypothesis, since the markedly reduced muscle cell potassium and low ratio of potassium to noncollagenous nitrogen (K/NCN) of patient EB indicate the incapacities of the cells to retain potassium. Since kidney tubular cells did not decrease the net secretion of potassium either during restriction or loading with this ion, it

would appear that they too were damaged and could not adequately defend body composition.

In patient AM, both tissue composition and renal function were better preserved. Another child, RJ, whose biopsy data are given in Table VI, had cystine-storage disease but was not a renal-potassium loser.

This interesting disease requires further study, with particular regard for the nature of the defect in cystine metabolism and the relationship of this amino acid or its congeners to potassium metabolism.

TABLE VI

Muscle Composition in Cystine-Storage Disease

Name	Age	Per 100 g DFFS§						
		Ecw	Icw	$[Na]_i$	$[K]_e$	$(K)_i$	$[K]_i$	$(K)_i/NCN$*
E. B.	$3^{2}/_{12}$	176	180	12.7	2.5	16.8	102	1.58
A. M.	$4^{4}/_{12}$	151	193	23.1	2.4	26.9	140	3.55
R. J.	$3^{8}/_{12}$	166†	230	26.5	2.7	35.1	153	—
		131‡	221	4.2	6.1	40.3	183	—
Controls (6)		139.2	220.2	19.1	4–5	35.6	159	3.69

* NCN—Noncollagenous nitrogen; [ ]e = concentration in extracellular water: [ ]i = content in intracellular water.
† After attempted dietary K depletion for 4 days.
‡ After excessive K intake for 5 days.
§ Dry, fat-free solids.

A PRIMARY RENAL DISORDER—THE NEPHROTIC SYNDROME

The nephrotic syndrome in children involves the glomerular basement membranes as well as the tubular cells. Although the renal functions are usually reduced at the outset,[39] this is not indicative of progressive or irreversible renal damage. Many afflicted children recover completely with little or no evidence of renal functional impairment.[40] The glomerular filtration rate and renal plasma flow become elevated with the diuresis of edema fluid such as that induced by steroid therapy.[41] Improved filtration is usually ascribed to expansion of plasma volume as a result of (a) increased hydrostatic filtration pressure and (b) decreased glomerular membrane permeability for albumin[42] with consequent increase in colloid osmotic pressure. During dextran infusions which expand plasma volume and raise osmotic pressure, a net increase in glomerular permeability for both water and albumin are observed. The concentration of serum albumin appears to be maintained at the expense of the extravascular pool of this protein.[43] Where the glomerular filtration rate does not increase despite marked plasma volume expansion, it seems likely that the elevated colloid osmotic pressure (from the combined effect of albumin and dextran) exerts a force of equal magnitude, but of opposite sign to the rise in filtration pressure. These effects of plasma volume and colloid osmotic pressure upon glomerular filtration indicate that the absolute levels of renal function in this syndrome are dependent upon a variety of hemodynamic factors as well as on the nature and extent of the potentially reversible lesions of the glomerular basement membrane and renal tubular cells.

In the edematous phase, thickening of the glomerular basement membranes and reduction in renal blood flow may cause reduction in glomerular filtration and, therefore, reduction of the tubular load of filtered solute. The reduced excretion of water and sodium during nephrotic edema cannot depend entirely on reduction in the filtered load, since glomerular filtration rate may not be significantly decreased in the young nephrotic. While edematous nephrotic children respond to oral water loading by enhanced excretion of dilute urine, in a manner entirely analogous to that occurring in the normal child,[44] increased amounts of circulating antidiuretic activity have been indirectly quantitated during nephrotic edema.[45] Presumably, enhanced water reabsorption superimposed on severe dietary sodium restriction may account for the increas-

ing hypotonic edema which often characterizes the active phase of the nephrotic syndrome in children. The endogenous stimulus for secretion of antidiuretic hormone is not known. Eder and associates[46] consider the diminished plasma volume a possible factor.

Reduced excretion of sodium during nephrotic edema is well known and can easily be demonstrated by administration of intravenous loads of the sodium salt of a nonreabsorbable anion such as para-aminohippurate. The increased reabsorption of sodium in this case appears to be proportional to the reduction in glomerular filtration rate and hence of the filtered sodium claiming excretion per unit of time. Figure 11 is constructed from load periods obtained in six nephrotic children as compared with three normal children: NE, SW, and NG.[47] The response of individual patients is of some interest. For example, in patient SJ (depicted by the open circles), in whom sodium loads were applied at filtration rates ranging from 20 to 88 ml/min/m², an almost straight-line relationship was apparent between the increase in filtration rate and increased urine sodium excretion. It will be observed, however, that diminished sodium excretion approximating 200 to 300 micromoles/min/m² during edema was not necessarily dependent upon reduced formation of the glomerular filtrate. When all data of excreted/filtered sodium (a derivate of reabsorption) were compared to the glomerular/tubular ratio (an index of the functional balance between the glomerular and tubular activities), no relationship between these was demonstrable (Fig. 12). The increased reabsorption of sodium in this syndrome probably depends on factors other than the glomerular-tubular imbalance.[46,48] Reabsorption of sodium by the renal tubules appears to be regulated by an adrenal cortical hormone,

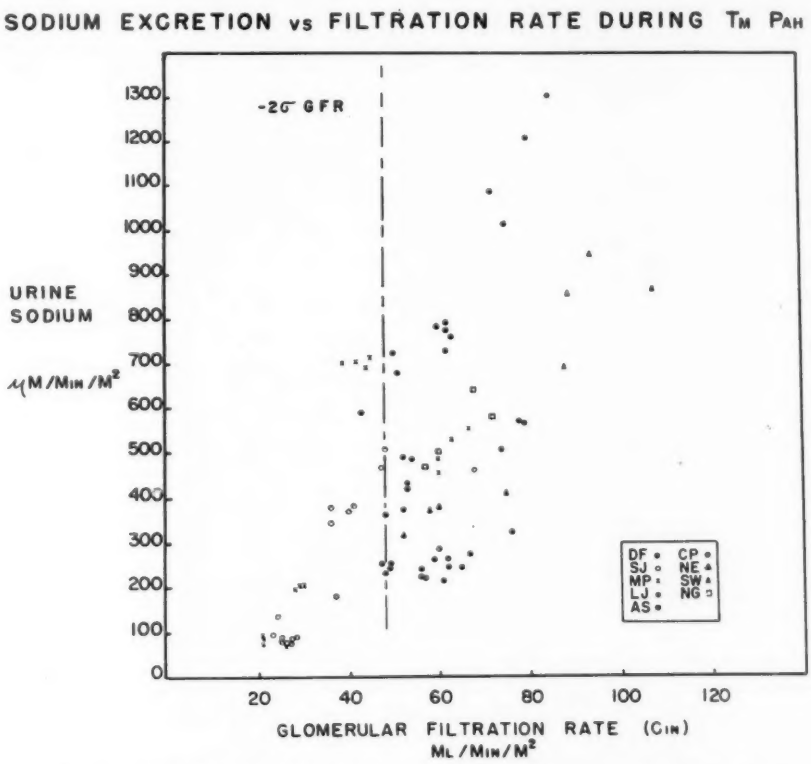


Fig. 11. Na PAH loads in nephrotic and normal children: sodium excretion.

aldosterone. Increased quantities of this hormone have been recovered from the urine during the edematous phase of the nephrotic syndrome, as well as during stringent sodium restriction or acute sodium depletion with hyponatremia.[35] The factor or factors responsible for the increased elaboration of aldosterone are not known.

on the other hand, that potassium secretion was demonstrated in several of the nephrotic children at normal levels of glomerular filtration (Fig. 13). A significant proportion of the potassium removed from the extracellular fluid and excreted in the urine was provided by or promptly replaced from the intracellular phase, according to calculation.[49] The per-

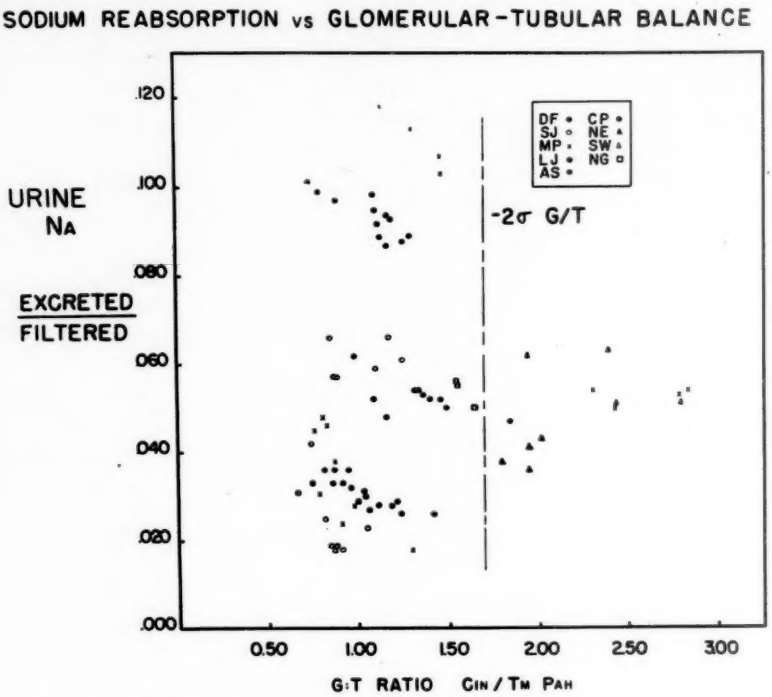


Fig. 12. Na PAH loads in nephrotic and normal children: sodium excretion.

When the sodium salt of a nonreabsorbable anion is infused into nephrotic children, the anion is promptly excreted but is usually covered in good part by an increased excretion of potassium rather than by sodium. The quantity of potassium recovered in the urine is often greater than that simultaneously filtered; thus active tubular secretion of potassium occurs in response to the anion load. This tendency to increased potassium secretion appears to be independent of either edema or reabsorption of sodium.[49] However, as suggested by Lauson,[50] potassium secretion can more readily be demonstrated at reduced levels of glomerular filtration. It will be noted, sistence of excessive potassium excretion during sodium loading, despite normal glomerular filtration rates and normal sodium excretion at the onset of diuresis and thereafter when the nephrotic child was nonedematous, suggested that potassium secretion was not necessarily dependent on excessive sodium reabsorption. It seemed possible that the tendency to renal removal of potassium might represent a homeostatic response to some cellular transport defect favoring potassium loss and indirectly conditioning sodium retention in support of osmolalities of the body fluids.[49]

It was subsequently shown that other mechanisms for acidification of the urine are present

in the nephrotic child,[51] in contrast to the usual competition between hydrogen and potassium for some common pathway of sodium exchange demonstrable in control subjects.[52] This was taken as further evidence for altered tubular electrolyte transport in this syndrome, presumably in defense of body fluids. The factor or factors initiating this defense remain unknown. vations on 24 urine samples were consistent with this inference.[54] Cellular catabolism (indicated by diminished tissue solids and nitrogen) presumably was occasioned by the disease which caused renal loss of protein and utilization of intracellular protein in support of the extravascular and circulating albumin pools, and for energy requirements. The potassium

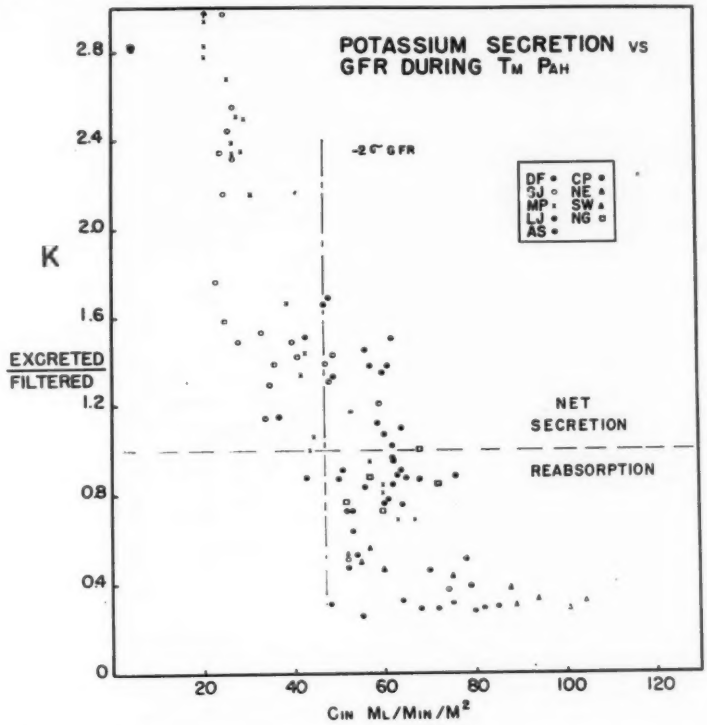


Fig. 13. Na PAH loads in nephrotic and normal children: potassium secretion.

Recent studies of body composition in young nephrotic rats provide evidence of loss of tissue solids and reduction in total body noncollagen nitrogen and potassium during edema as compared with nonedematous, pair-fed controls.[53] The intracellular concentration of potassium in muscle was reduced, largely as a result of intracellular overhydration. Since extracellular potassium concentrations were not increased and diarrhea did not occur, it seems likely that larger quantities of potassium were removed by the kidneys of the edematous rats than were excreted by their pair-fed, non-nephrotic controls. A few observed released from the destroyed cells must have been partially utilized by surviving cells and the excess rapidly excreted, since serum concentrations were not elevated, cell potassium contents were normal, but body content was reduced. Thus, the enhanced renal excretion of potassium by nephrotic rats would serve to defend body composition, as suggested for the human.[49]

Evidence that catabolism of cells provides a ready source of potassium, at least, for surviving cells is indicated by the data of Table VII.[55] The data represent observations on groups of three pair-fed rats having maximum sodium

TABLE VII

Group	No. of rats	Muscle, per 100 g DFFS					Total body				
		Ecw*	Icw	$(Na)_e$	$[Na]_e$	$[K]_i$	H_2O	DFFS	Na	K	NCN
		ml	*ml*	*mM*	*mM/l*	*mM/l*	*ml*	*g*	*mM*	*mM*	*g*
Nephrotic rats, normal diet	4	95	288	15.3	16	129	31.9	9.7	2.4	2.8	0.85
Pair-fed controls, normal diet	5	58	282	9.3	24	126	34.7	11.4	2.5	3.3	1.00
Nephrotic rats, low Na, no K diet	3	117	309	18.7	23	111	26.3	7.8	2.1	2.1	0.62
Pair-fed controls, deficient diet	6	70	279	12.3	43	99	29.5	9.2	2.4	2.4	0.78

* See previous tables for explanation of symbols.

reabsorption induced by low sodium, potassium-free diets. The nephrotic syndrome was induced in one member of each group and the remaining two rats served as diet controls. It is apparent that the cellular concentrations of sodium and potassium were more nearly normal in the nephrotic rats than in their controls, although their total body content of solids, potassium, and noncollagenous nitrogen were reduced.

It is of considerable interest that severe cellular potassium depletion in nephrotic rats was not associated with accumulation of intracellular sodium on a low sodium intake, although this was observed in the pair-fed controls. If accumulation of intracellular sodium in potassium deficiency is dependent on exchange of $Na^+ + H^+$ for K^+, as suggested by Cooke,[56] some aberration in this mechanism characterizes the muscle cell, as well as the kidney tubule cell, in the nephrotic syndrome.

CONCLUSIONS

From the foregoing, it seems apparent that the structure of the body fluids depends upon the effectiveness with which the kidneys regulate the reabsorbate which comprises the extracellular fluid. This major regulatory defense of body composition is supplemented by the continuous exchange taking place between the interstitial and intracellular fluids. In general, it seems that the kidneys always tend to function with the maximum efficiency of which they are capable. Intrinsic disease limits their efficiency. Extrarenal cellular disorders demand renal adjustments which serve to limit the distortion of body composition. While these compensatory mechanisms often may suggest renal insufficiencies, improved knowledge of the interrelationships between the kidney and extrarenal cell functions undoubtedly will afford a better perspective.

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Calcium and the Kidney

By DANIEL S. KUSHNER, M.D.*

THE METABOLISM of calcium and implications of its derangement in functional and structural renal alterations offer an imposing challenge. Recent observations by the clinician, physiologist, biochemist, biophysicist, and pathologist, and the availability of radioactive tracer techniques, have contributed much, while opening new avenues for investigation. Yet much remains to be explored and understood. This review is a presentation of current concepts regarding relationships between calcium metabolism and the kidney in the light of recent work and from the point of view of calcium nutrition in its broadest sense. In this discussion emphasis will be on problems of nutritional requirements for calcium, renal mechanisms for calcium excretion, calcific renal injury, and states of altered calcium metabolism as an indirect consequence of disordered renal excretory mechanisms.

NUTRITIONAL REQUIREMENTS FOR CALCIUM

The principal dietary sources of calcium are milk and its derivatives. Foods containing oxalic or benzoic acids, such as spinach, beet greens and cranberries, decrease the absorption of calcium, since the oxalate and benzoate salts are insoluble. Moreover, a high ratio of phosphorus to calcium in the diet also depresses calcium absorption, because calcium phosphate is less soluble in the presence of an excess of phosphate ion. Similarly, the ingestion of whole-grain cereals, in which phosphorus is largely in the form of phytin, leads to precipitation of insoluble calcium phytates with resultant fecal loss of both the calcium and phosphorus.[1] In uremia, phosphorus which is retained by the failing kidney, is excreted into the bowel in high concentration; insoluble calcium phosphate salts are precipitated and thus absorption of alimentary calcium is prevented.

Calcium Absorption

Since calcium salts in foods are not readily soluble in neutral or alkaline solution, their absorption occurs largely in the upper part of the small intestine where the contents are still somewhat acid. Thus calcium absorption is in part dependent on maintenance of a normal gastric acidity. Recently Ca^{45} tracer studies in rats[2] demonstrated that all of the calcium in the proximal two thirds of the small intestine is promptly absorbed. After four hours, most of the nonabsorbed calcium is found in the distal one third of the small intestine and colon. In the next 24 hours even this portion is slowly absorbed. Vitamin D increases the amount of calcium absorbed from the small bowel, but principally alters the slow phase of absorption from the distal ileum and colon. Protein also increases calcium absorption. In the presence of steatorrhea, calcium forms highly insoluble soaps of fatty acids which precipitate in the alkaline medium of the small bowel, resulting in fecal calcium loss. In general, the absorption of calcium is largely conditioned by the status of calcium balance (status of depletion) rather than by the dietary level. Absorption and retention of calcium are increased in calcium-depleted animals; utilization efficiency decreases with increased dietary calcium intake.[3–5]

From the Department of Medical Education and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

* Associate Director of Medical Education, Cook County Hospital and Instructor in Medicine, Northwestern University Medical School.

Calcium is never completely absorbed, regardless of intake. Moreover, in addition to that in food, a considerable contribution to the amount of calcium entering the bowel is made by the digestive secretions. An average of 8 liters of digestive secretions contain an average of 8 mg of calcium/100 ml. Thus from 0.3 to 0.8 g (mean 0.65 g) of calcium is secreted into the bowel daily, and unless conditions favor its absorption, much of this calcium is excreted.[6–7] An unavoidable loss of calcium from the bowel results from its precipitation as insoluble salts of carbonate, phosphate, or fatty acids in the alkaline intestinal fluids. This explains why fecal excretion may greatly exceed intake, especially when the calcium intake is low. Thus 75 to 90 per cent of calcium excreted appears in the stool and only 10 to 25 per cent in the urine.

Calcium is absorbed into the plasma and is distributed through the other extracellular fluids of the body in amounts decreasing with the protein content of the given fluids. The level of plasma calcium (10 mg/100 ml) also tends to vary in the same direction as the serum protein. The absorbed calcium not retained in extracellular fluids is quickly deposited in bone, under regulation of the parathyroid glands. An equilibrium is established between skeletal calcium deposition and depletion. Osteoporosis of old age may result from several factors, including diminished exercise-induced skeletal stresses, diminished circulation, atrophy of bone matrix, or ingestion of insufficient calcium to permit replacement of normal loss. The effect of a long-continued low calcium intake will be aggravated if the customary diet is acid in ash, requiring additional body base for neutralization. More rapid and general loss of bone mineral occurs in acidosis or with an excessive production of parathyroid or thyroid hormone. Excessive intake of vitamin D or dihydrotachysterol likewise results in an outpouring of mineral from bone.

In individuals who are not retaining calcium the urinary calcium increases with an increase in calcium absorption,[8] while in children increased calcium absorption results in increased retention.[9]

Daily Requirement of Calcium

As stated above, the minimum requirement will depend on the state of health of the individual and the efficiency of intestinal absorption. Febrile illness is accompanied by decreased gastric acidity and calcium absorption. Chronic, low-grade, upper respiratory infections definitely decrease the absorption of calcium in infants and children for weeks or months.[1]

During growth the calcium requirement is based on the skeletal need, which in turn is based on the calcium content of the adult skeleton, with a spread according to the proportionate growth rate during each year of the growth period. Estimates have varied from 1000 to 2000 g of calcium contained in a completely mineralized skeleton. Thus the calcium retention in children from a given intake varies with the rate of growth common for the age of the child. Human milk contains 320 and 130 mg/l respectively of calcium and phosphorus, compared with 1180 and 930 mg/l in cow's milk. Only small amounts of calcium are excreted in the urine of breast-fed infants (less than 10 mg/day). The total amount absorbed is insufficient to maintain the mineral content of the rapidly growing skeleton at its birth percentage. Therefore, the prematurely born infant, lacking the final (in utero) period of storage of skeletal calcium, is especially vulnerable to calcium deficiency, which may be compensated for by supplements of powdered skimmed milk and vitamin D.[1]

Supplements of vitamin D (to 350 I.U. daily) given to an infant fed cow's milk increase the absorption of calcium from 10 to 40 per cent of the intake, and no greater absorption can be achieved by larger doses of vitamin D. Requirements are greatest during periods of maximal skeletal growth, from approximately age 14 to 18 years. Using tracer Ca^{45}, experimental parallels are found in the observation that rats at 6 to 8 weeks absorbed more calcium than rats 10 to 20 weeks old.[10]

Increased requirements for calcium during pregnancy and lactation stem from needs of the fetal skeleton (which stores approximately 25 g during the last trimester), maternal urinary calcium losses, loss of maternal calcium to

the placenta, and finally the considerable loss of 320 mg of calcium per liter of human milk. Thus it is estimated that a daily intake of 1500 mg calcium during the second half of pregnancy, and of 2000 mg during lactation, is necessary to maintain calcium balance.[1]

Estimates of calcium requirements in adults have varied widely in various countries, presumably depending upon the level of calcium customarily ingested. Thus, requirements are greater in individuals accustomed to a high calcium diet. In the United States healthy adults are in calcium equilibrium when the calcium intake is 10 mg/kg of body weight (0.5 to 0.8 g calcium daily). The National Research Council Recommended Allowance (1953) of 0.8 g daily can be achieved by ingestion of one pint of milk, together with cheese, ice cream, or cream, or three glasses of milk daily. Requirements for postmenopausal women appear to be considerably higher, 14 mg/kg of body weight.[11]

The relationship between dietary calcium and phosphorus may be of considerable importance. Dietary imbalance, with low phosphorus cereal diet, has been shown to promote renal lithiasis; under such circumstances stones will be prevented by the addition of both phosphate and vitamin A to the diet.[12] A cereal diet may be in effect a low phosphorus diet because of the low availability of phosphorus present (as much as 70 per cent) as esters of inositol).[13,14]

RENAL MECHANISMS FOR CALCIUM EXCRETION

Until recently, little was known concerning the renal excretion of calcium except that the total excretion can be altered by varying the calcium and phosphorus intake, the acid-base forming properties of the diet, and the state of parathyroid function.[15] The obstacle to studies of renal transport lies largely in the complex physicochemical state of serum calcium. Only half of the normal plasma calcium (9–11.5 mg/100 ml) is diffusible; the remainder exists in combination with plasma proteins. The dissociation of incompletely ionized calcium proteinates depends on protein and calcium ion concentration, pH, temperature, and on the albumin-globulin ratio. Moreover, although calcium chloride is probably a completely dissociable salt, some of the plasma calcium may exist in combination as poorly ionized nonprotein complexes such as calcium citrate.[16]

Such complexes may account for no more than 0.5 mg/100 ml of the total plasma calcium, the remainder being equally divided between calcium proteinate and physiologically active calcium ion.[17,18] The amount of ionic calcium in relation to plasma protein levels may be calculated from a nomogram.[19] It is of considerable theoretical interest that other ions, such as magnesium, compete with calcium for combination with serum albumin in a mass-action effect.[20] Thus an increase in magnesium concentration may diminish the amount of calcium bound to protein, thereby increasing its plasma concentration and its urinary excretion.

Physiologic control of plasma calcium concentration appears related chiefly to maintaining a constant concentration of physiologically active ionized calcium through the parathyroid secretion. Administration of parathyroid hormone to normal dogs raises total serum and filtrable calcium and increases the rate of both tubular reabsorption and excretion. The former is attributed to the increased filtered load, as a consequence of hypercalcemia from mobilized skeletal stones.[21] Calcium clearance data indicate that calcium is actively and almost quantitatively (99 per cent) reabsorbed by the renal tubules, independent of the rate of urine flow, but with no tubular maximal resorptive capacity (reabsorption being depressed at high serum calcium levels).[22,23]

However, Wolf and Ball[24] concluded that there is no effective "threshhold of retention" and that the plasma concentration of calcium is not exclusively regulated by renal function.

Factors influencing the excretion of calcium in urine in normal persons[9] include calcium intake, skeletal size, acid-base regulation of the body, and factors assumed to be the resultant of various body hormones, including parathyroid, thyroid, and the sex and pituitary hormones. Hence the normal range of variation of urinary calcium is far wider than is

usually appreciated. The maximal normal excretion at any level of intake per kilogram of body weight is approximately 10 times the minimum. Thus, two individuals of equal size, given identical diets may excrete from 25 to 250 mg of calcium daily.

A relationship apparently exists between the renal excretion of calcium and other electrolytes. Infusion of calcium induces prompt sodium and chloride diuresis, as a result of reciprocal changes in the rate of tubular reabsorption of sodium and chloride.[25] Parathyroid extract and vitamin D, which elevate the level of serum calcium and increase phosphate excretion, also increase the excretion of sodium and chloride.[26] Finally, in hypoparathyroid tetany, low urinary excretion of calcium and phosphate are accompanied by diminished sodium, chloride, and urate clearance.[26]

Hypercalcemia without Hypercalciuria

The calcium normally excreted in the urine is a remarkably small portion of the amount filtered. A simple calculation reveals that 5 to 7 mg of ultrafiltrable calcium is present in 100 ml of serum; 125 ml of glomerular filtrate (ultrafiltrate of serum) is presented to the renal tubules per minute (180 liters/day), and therefore some 9 to 12.5 g of calcium is daily presented to the renal tubules for excretion. Since normally only 100 mg is excreted per 24 hours, then 99 per cent of calcium filtered must be reabsorbed.[27] This, therefore, together with the observations that marked increases in urinary calcium excretion (for example, in thyrotoxicosis, acidosis, acute osteoporosis) are not reflected in changes in serum calcium, suggests a specific renal excretory mechanism for calcium excretion.

As the level of serum calcium rises the proportion of calcium bound to protein can be greatly increased, with little change in the ultrafiltrable calcium. At extremely high serum calcium levels, the portion which is ultrafiltrable may decrease. This is particularly true at higher levels of serum phosphorus.

However, calcium and phosphorus are not at saturation levels in normal serum; the level of calcium in ultrafiltrate has been increased to 20 mg/100 ml before decrease in filtrability occurs[27]; at higher pH, calcium precipitation occurs at lower levels. Thus, when the concentrations of serum calcium and phosphorus are such that ultrafiltrable calcium is reduced, these complexes act as foreign bodies and may be precipitated in tissues. The changes in calcium and phosphorus levels in response to alteration of either are thus the results of physiologic mechanisms, rather than a physicochemical necessity to maintain inverse proportions, according to the relationship,

$$\frac{Ca^{++} \times HPO_4^{=} \times HCO_3^{-}}{pH} = K$$

(In view of the large number of excellent reviews on parathyroid physiology,[28–33] only brief reference will be made in this paper to the influence of parathyroid function on calcium metabolism.)

Citric Acid and Calcium Excretion

Evidence of the importance of citric acid in the metabolism and renal excretion of calcium is increasing.[34–39] The citric acid content of human blood varies from 1.5 to 4.0 mg per 100 ml and its normal urinary excretion varies from 0.25 to 1.0 g/day. Increased alkaline-urine and decreased acid-urine excretion are apparently due to changes in tubular reabsorption of citrate dependent on pH. Serum citrate concentrations are increased in hypercalcemic states due to hypervitaminosis D, hyperparathyroidism, or other causes, and are decreased in hypoparathyroidism with hypocalcemia. Administration of parathyroid extract or vitamin D to the hypoparathyroid individual increases the serum level and urinary excretion of citrate, paralleling changes in calcium. Citrate has also produced a vitamin D-like effect in the treatment of infantile rickets. Experimentally, its repeated use has resulted in osseous changes similar to those produced by parathyroid hormone and, significant increases in urinary calcium. Conversely, the injection of calcium reduces urinary citric acid excretion. Since the kidney is the main site for removal of circulating citrates, the transient hypercalcemia which occurs following nephrectomy is explained by a di-

minished ability to remove citrate from the blood.

Experimentally, a low phosphorus diet led to increased urinary excretion of calcium and citric acid and extensive calcium citrate urinary stone formation.

Citrate is not ordinarily reported as a constituent of stones. However, citric acid can be demonstrated in stones in amounts up to 1.5 per cent, suggesting that the role of citrate may be limited to the formation of the nidus upon which phosphates and other salts are precipitated.

The renal excretion of citrate is decreased in patients suffering from nephrolithiasis. Some question the significance of this observation, because citrate is utilized by bacteria and thus rapidly disappears in infected urine.[34] The concentration of citrate in urine could certainly influence the solubility of urinary calcium. It is estimated that in urine containing 100 mg of calcium and 480 mg of citrate per liter, at neutral pH more than half of the calcium would form a complex with citrate. Clinical application is limited since, paradoxically, administration of alkalinizing salts is contrary to the accepted practice of attempting to maintain an acid urine in patients with calcium stones. Finally, however, the administration of acetazoleamide (Diamox®), increases urinary pH and reduces urinary citrate excretion of rats, and may cause precipitation of calcium in the kidneys.[39] It is concluded that the complexing of calcium by urinary citrate, forming undissociated calcium citrate, is of importance in the prevention of calcium precipitation in the kidney. Furthermore, the nature of the precipitate and its location in the renal tubule is dependent upon the concentration of phosphate in the urine. Thus the concept of a relationship between urinary citrate and calcium stone formation remains current.

Calcium Gout and Chemical Uremia

The concept of chemical uremia originated with Virchow,[40] who described calcium metastases to the kidney causing uremia as a consequence of destructive skeletal lesions. The causes of fatal renal insufficiency related to calcific renal injury may be classified as follows:

(1) Diseases of primary renal injury, not associated with hypercalcemia or hypercalciuria, including chronic glomerulonephritis, chronic pyelonephritis, renal tubular acidosis, mercurial and sulfonamide nephrosis; in these conditions a primary renal disease leads to dystrophic calcification in necrotic renal tissue.

(2) Diseases associated with hypercalcemia and metastatic calcification but not with hypercalciuria, including the so-called Burnett Syndrome, and hypochloremic alkalosis of pyloric obstruction.

(3) Diseases constantly associated with hypercalcemia and sometimes with hypercalciuria and metastatic calcification, including sarcoidosis, hypervitaminosis D, primary hyperparathyroidism, acute osteoporosis, Paget's disease (especially with immobilization), multiple myeloma, and osteolytic skeletal lesions due to metastatic carcinoma, sarcoma, or malignant lymphoma.

(4) Conditions of idopathic hypercalciuria.

Impairment of renal function or even fatal renal insufficiency in hypercalcemic individuals with sarcoidosis or Hodgkin's disease is rare, though actual renal involvement by sarcoid or Hodgkin's granulomas occurs in as many as 45 and 13 per cent, respectively,[41] thus suggesting the possibility that functional renal injury is related in some cases to persistent hypercalcemia. Similarly, vitamin D intoxication and the Burnett Syndrome (see below) commonly lead to fatal or reversible renal insufficiency in the absence of antecedent renal disease. Severe renal functional impairment is extremely frequent in hyperparathyroidism, often in the absence of radiologically demonstrable nephrocalcinosis. In some instances, early resection of the parathyroid adenoma has resulted in varying degrees of recovery of renal function. The rare syndrome of parathyroid poisoning, with serum calcium levels in excess of 20 mg per 100 ml has also been associated with marked impairment of renal function.[28, 29]

FUNCTIONAL RENAL INJURY DUE TO HYPERCALCEMIA

Numerous clinical observations attest to a relationship between hypercalcemia and compromise of renal function.[42–48] In addition to gastrointestinal symptoms (anorexia, nausea, vomiting, constipation) and cerebral signs (apathy, obtunded mentation, and coma), hypercalcemic individuals also manifest oliguria, azotemia, and uremic death.

The appearance of renal insufficiency at a time when metastatic renal calcification may be unimpressive suggests that abnormalities are induced by hypercalcemia in glomeruli or in the renal vasculature which are not appreciated by microscopic examination.[49]

At its onset, hypercalcemia is probably always associated with hypercalciuria. Renal injury, however, is brought about by hypercalcemia: the excessive concentrations of calcium in glomerular filtrate and tubular urine may initiate tubular calcification leading to renal functional impairment. Thus the ability of the damaged kidney to excrete a calcium load may be diminished, and hypocalciuria may be a late finding in hypercalcemic states. Finally, the presence of associated renal disease increases the hazards of hypercalcemia.[50] Not only are renal functional abnormalities of some degree characteristic of the hypercalcemic state, but remission of the hypercalcemia may result in prompt increase in the urinary output and subsidence of azotemia. Clinical and pathologic considerations relating to nephrocalcinosis have been the subject of recent reviews.[51–52]

IDIOPATHIC HYPERCALCIURIA

Albright and associates[53] observed 22 patients with a syndrome of normal serum calcium, low serum phosphorus, increased urinary calcium excretion, and, in most instances, staphylococcal pyelonephritis. None of these patients had hyperparathyroidism. Analysis of the renal stones revealed a similarity in composition to those in patients with hyperparathyroidism and renal tubular acidosis. Most (79 per cent) contained no magnesium or ammonium (as evidence of infected alkaline urine), and their content of calcium phosphate presumed an origin in hypercalciuria. The pathogenesis suggested was staphylococcal pyelonephritis causing renal tubular damage, resulting in diminished tubular reabsorption of calcium, consequent loss of calcium and phosphate in the urine, with diminished blood phosphate and unaltered serum calcium levels.

NEPHROLITHIASIS

Calcium is a component of 90 per cent of all primary urinary calculi and alone or with magnesium comprises the greater portion of their total cation content. Recently, increasing attention has been given to physicochemical interrelationships between urinary crystalloids and organic suspensoids and the role of protective colloids in maintaining the constituents of the urine in solution.[54,55] Urinary calculi are composed of an organic matrix (of mucous character) and crystalline material (derived from supersaturated fluid). A concept was developed of labile and stable protective colloids, which hold stone-forming salts in solution in the urine. Many have stressed the role of vitamin A deficiency in producing alteration of the renal epithelium and thereby affecting the excretion of urinary colloids. Thus a calculus consists of a crystalline nucleus surrounded by amorphous or crystalline colloidal precipitates.

Despite the daily urinary excretion of up to 4 g of precipitable mineral salts, the calcium content of urine can be doubled without causing precipitation. In the absence of metabolic or neoplastic skeletal disease, most patients with urinary calculi do not have hypercalciuria. On the contrary, many patients with acidosis, myelomatosis, hyperparathyroidism, and hyperthyroidism consistently have hypercalciuria without the formation of urinary calculi. Moreover, crystalluria frequently is not associated with the formation of calculi. The controversy as to whether or not urine is a supersaturated solution of relatively insoluble salts appears to center about the fact that a mutual increase of solubility occurs in complex solutions, such as urine, which greatly reduces the degree of such supersaturation when compared with a simple aqueous solution of a single component.[56] For example, uric acid is seven times more soluble in sea water than in distilled water.

Therapy of Renal Lithiasis

Basic to the therapeutic approach to urinary lithiasis is a search for constitutional disease and correction of underlying metabolic disorders. The necessity for investigation to exclude hyperparathyroidism has been repeatedly emphasized because of the frequency with which parathyroid adenoma first makes its presence known by the production of urolithiasis. Unfortunately, in the vast majority of instances of nephrolithiasis, no definable metabolic abnormality can be found.

The problems relating to hypercalciuria and nephrolithiasis include (1) urinary tract infections; (2) osteoporosis, either idiopathic or secondary to immobilization, the postmenopausal state, senility, Cushing's disease, and acromegaly; (3) overdosage with vitamin D or AT.10; (4) sarcoidosis; (5) metastatic malignancy to bone and multiple myeloma; (6) Paget's disease. It has been estimated that in acute states (immobilization), urinary loss of calcium may total 24 g in six weeks.[57]

Attention to multiple factors in the therapy of nephrolithiasis has been emphasized. These include vitamin A deficiency, the frequency of accompanying urinary tract infection (only 13 to 26 per cent of stone-formers have sterile urine), and urinary stasis, in addition to metabolic problems.[58] A systematic approach to the patient with recurrent urolithiasis thus must include search for a history of alkaline medication or vitamin D ingestion, bacterial culture of the urine and elimination of infection, both local and genitourinary, elimination of stasis, maintenance of a large fluid intake and brisk urine flow, correction of metabolic disorders, administration of vitamin A, chemical analysis of the calculus, and test of urinary pH.

Aluminum hydroxide gels are of value in diminishing urinary phosphate excretion by forming insoluble aluminum phosphate in the bowel and thereby preventing absorption of phosphate and favoring more complete tubular reabsorption of phosphate. Estrogenic hormones have been recommended on the basis of their demonstrated effect in enhancing urinary excretion of citric acid, while reducing that of calcium, thus increasing the solubility of the latter. A low phosphorus diet has been advocated on the theory that decreased intestinal absorption of phosphorus results in lowered serum level, more complete tubular reabsorption of phosphorus, a reduced primary excretion of phosphorus, and less chance of precipitation of calcium phosphate salt.[59] Paradoxically, animal studies indicate that a low phosphorus diet leads to production of calcium citrate calculi, as a result of increased intestinal absorption of calcium, elevation of blood ionized calcium, its combination with citrate, and increased renal excretion of both citrate and calcium.

The level of urinary calcium excretion may be crudely estimated by use of the Sulkowitch reagent, or may be quantitatively determined. The latter must be done after the patient has come into balance on a low calcium (Bauer-Aub) diet of about 140 mg of calcium per 24 hours. Twenty-four-hour urine collections made after the third or fourth day of diet should normally contain no more than 150 mg of calcium, and amounts in excess of 200 mg are distinctly abnormal.

The role of infection in urinary lithiasis is of great importance.[60–61] The organisms involved in the formation or reformation of renal stones are the urea-splitting bacteria, *B. Proteus* and *Micrococcus pyogenes*. In addition, *Psuedomonas*, *influenza*, *diphtheroids*, and *E. Coli* strains have been incriminated. The stones formed in association with infection are invariably calcium stones of the apatite variety, that is, calcium carbonate, calcium phosphate, and magnesium ammonium phosphate.

The splitting of urea with production of ammonia results in a highly alkaline urinary pH, changing the soluble monocalcium phosphate to the more insoluble dicalcium phosphate. Thus Howard[60] has suggested this simple test for the presence of urea-splitting organisms: To one of two tubes of normal sterile urine, add a few drops of the patient's urine and incubate overnight. Test the pH of both urines with nitrazine paper. The control urine may perhaps become slightly more alkaline by virtue of the loss of Co_2 by diffusion. However, if the pateint's urine becomes very alkaline, this must be due to the presence of growth of urea-splitting organisms.

Recent attempts at rational therapy have been directed toward alteration of urinary colloid-crystalloid relationships by the use of hyaluronidase therapy. Considerations concerning hyaluronidase therapy include adequate renal function, and response to a trial injection by significant clearing of urinary turbidity, decrease of sediment, and reduction in urinary surface tension to normal or below. Results of experience in 44 patients treated for 30 to 47 months suggest improvement in 31, with formation of calculi controlled in 20 and reduced in 11.[55]

Among substances in the urine which form soluble complexes with calcium are glucuronic acid and its glycosides. In the presence of infection, as has been demonstrated with *Staphylococcus albus*, such solubilizing substances as urinary glucuronides are inactivated or destroyed. Calcium carbonate and calcium phosphate, insoluble in water at neutral or slightly alkaline pH, are solubilized in the presence of glucuronides.

Such observations have led to attempts at treating recurrent calcium urolithiasis by administering agents which increase the urinary excretion of glucuronisides.[56] The most common compound which is excreted as a conjugate of glucuronic acid is salicylic acid or any of its salts. In *in vitro* experiments, a crude glucuronide preparation increased the solubility of calcium phosphate solutions by 30 per cent. Preliminary evaluation of therapy consisting of 2 g of aspirin daily showed considerable promise, and the output of urinary glucuronides significantly increased. Penicillin and some sulfonamides will increase glucuronide excretion, and the administration of large doses of salicylates carries with it the risk of hypercalciuria. Control of bacterial urinary tract infection, maintenance of a brisk urine flow, and low calcium dietary intake are emphasized as important ancillary factors.

CALCIUM METABOLISM IN CERTAIN SYNDROMES

The So-called Burnett Syndrome

In 1949 Burnett and associates[62] described six cases of hypercalcemia with low urinary calcium output, alkalosis, and impaired renal function in the face of normal or only slightly increased blood pressure—a syndrome following prolonged ingestion of large amounts of milk and absorbable alkalis in the treatment of peptic ulcer. A significant observation was that of two types of ocular changes: (1) hazy, granular or subepithelial corneal deposits running concentrically with the limbus on either the nasal or temporal side or both, designated as band keratopathy, and (2) small glasslike particles in the conjunctivae of the palpebral fissure area. Biopsy in one case showed amorphous material (calcium salt) beneath the conjunctival membrane. Other metastatic calcifications occurred in the kidney, dura mater, tentorium, falx, diaphragm, costal cartilages, bronchial tree, subcutaneous nodules in elbows, hands, and knees, tendons, and blood vessels; in addition, the cancellous bones were dense and periosteal new bone formation was frequent. The syndrome must be distinguished from hypercalcemia with renal failure due to acute osteoporosis, hypervitaminosis D, sarcoidosis, myelomatosis, carcinomatosis with bone involvement, and hyperparathyroidism, and from metastatic calcification due to other causes such as chronic renal insufficiency with acidosis in young persons and chronic renal tubular acidosis.[63] Burnett *et al.* emphasized the importance of high phosphorus as well as the high calcium content of milk in producing the syndrome, since withdrawal of milk and alkalis was frequently followed by a prompt fall in serum phosphorus level. Since the original description many such instances have been reported.[64–70]

Among these, however, have been included instances of identical clinical and biochemical syndromes with irreversible renal failure, in which necropsy revealed the presence of parathyroid adenoma or hyperplasia.[71–78] The feature of normal or low urinary calcium excretion can hardly be used as a differential point in the exclusion of hyperparathyroidism, in the face of renal insufficiency with consequent diminution in the ability of the damaged kidney to excrete calcium. Therefore, whether such parathyroid hyperplasia is secondary to chronic renal insufficiency or is actually primary frequently remains moot. Indeed, several observers have recently challenged the

validity of the Burnett syndrome, re-emphasizing the difficulties in differential diagnosis and suggesting that at least some cases actually result from parathyroid hyperfunction (due to adenoma or hyperplasia), accentuated by high calcium intake and alkalosis, and complicated by renal insufficiency, with resultant atypical biochemical changes. The hypercalcemia and metastatic calcification truly induced by high calcium and absorbable alkali intake, or by chronic alkalosis alone, should promptly regress following withdrawal of milk and alkalis.[79–81] Of particular interest in this regard are the reports of cases of "acute hyperparathyroidism with classical symptomatology of parathyroid poisoning" in patients with chronic peptic ulcer under long-term treatment with milk and alkalis. In one a parathyroid adenoma, in another primary *wasserhelle* hyperplasia and supernumerary parathyroids were found at necropsy; both had extensive metastatic calcifications. The danger of calcium or alkali ingestion in primary hyperparathyroidism has been emphasized. A number of observers have pointed out an association between hyperparathyroidism and peptic ulcer, giving an incidence as high as 24 per cent of patients with hyperparathyroidism.[82–84] In doubtful cases, only parathyroid exploration may settle the issue. The syndrome of hypercalcemia without hypercalciuria or hypophosphatemia, calcinosis, and renal insufficiency in patients with peptic ulcer should direct attention to occult hyperparathyroidism.[71–78]

Idiopathic Infantile Hypercalcemia

An unusual form of persistent hypercalemia in infants, for which no cause can be found, was first described in 1952.[85,86] It is characterized by hypercholesterolemia, osteosclerosis, nephrocalcinosis, and retardation of physical and mental growth. A benign form exists, with good prognosis. The more severe type (4 deaths of 10 reported) is associated with a characteristic facies, described as "elfin", with squint, hyperkinesis, small skull, craniostenosis, dwarfing, and mental retardation. First symptoms appear from birth to 12 months, and the hypercalcemia has been recognized from ages 7 to 30 months. Nitrogen retention invariably accompanies the hypercalcemia and other evidences of impairment of renal function. Hypercholesterolemia has accompanied the hypercalcemia in 7 of 10 cases. Blood inorganic phosphorus levels are occasionally above normal, correlating with the blood urea nitrogen retention. Alkaline phosphatase levels tend to be low. Hypertension and systolic murmurs have been observed. Radiologic and pathologic evidence of both increased density and thickening of bones are described in the base of the skull, metaphyses and epiphyses of long bones, vertebral bodies, ribs, and iliac crests, similar to that produced by vitamin D poisoning, but without changes to suggest Albers-Schönberg's disease. Albuminuria and urinary sediment changes are frequent, and amino acid excretion is normal. Histologically the kidneys have been observed to be contracted, showing severe nephrocalcinosis with ischemic necrosis, fibrosis, and widespread calcification, involving both glomeruli and tubules. Metastatic calcifications frequently involve blood vessels, myocardium, brain, meninges, lungs, and stomach.[85–95]

No associated congenital malformations involving skeleton, kidneys, or heart have been found. The syndrome and pathologic changes appear to be the result of renal damage consequent to long-standing hypercalcemia. In the absence of clear evidence to support an etiology of high vitamin D intake or alkaline medication ingestion by the mothers or by the infants, it has been suggested that an abnormal sensitivity to vitamin D is determined by individual metabolic requirements or by growth disturbance. Therapy has been successful with low calcium diet, but cortisone has been reported to be efficacious in reducing the serum calcium levels and thereby relieving symptoms. Cortisone apparently acts by increasing fecal excretion of calcium (decreasing its absorption from the bowel) and perhaps also by effecting a redistribution of calcium within the body.

The syndrome appears to occur most frequently in Great Britain, is rare in Sweden, and has not yet been reported from the United States. It has been likened to the hypercalcemia of sarcoidosis and vitamin D intoxi-

cation, both in its pathogenesis and therapy. Of interest is the tendency toward low alkaline phosphatase levels (also observed in hypervitaminosis D), as well as the hypercholesterolemia accompanying elevated serum calcium, also observed with calciferol administration.[96-97]

Cortisone and Calcium Metabolism

Cortisone has an antagonistic effect on calcium metabolism.[98,99] The net effect of cortisone is to produce a negative calcium balance, presumably by a combination of diminished calcium absorption, increased calcium excretion, and lowered serum protein-calcium binding capacity.

A practical application of the cortisone effect has been made in the differential diagnosis of obscure hypercalcemias. Cortisone is administered at a dosage level of 150 mg/day for 10 days; serium calcium is determined at 5, 8, and 10 days during cortisone administration. The hypercalcemia of hyperparathyroidism is not altered, but that of sarcoidosis, vitamin D intoxication, and idiopathic hypercalcemia of infants rapidly diminishes to normal serum calcium values. Thus cortisone has been suggested as a specific antidote for vitamin D intoxication. The availability of such a test is particularly important in patients with impaired renal function in whom phosphate excretion studies have limited or dubious validity.[99]

The catabolic action of cortisone in producing negative nitrogen and calcium balances may be neutralized in males with androgenic substances and in females with estrogenic substances, which rather promptly produce positive calcium balances in individuals receiving cortisone therapy.[100]

Osteomalacia and Late Rickets

Albright and his group[101] defined osteomalacia ("adult rickets") as a disorder of bone tissue characterized by a failure of calcium salts to be deposited promptly in the newly-formed (normal) bone matrix (osteoid). Among the conditions characterized by either low serum calcium or phosphorus, high alkaline phosphatase, and demineralized softened bones are (a) *vitamin D lack*, due to (1) deficiency, (2) resistance to vitamin D, or (3) decreased vitamin D absorption resulting from steatorrhea; (b) *renal acidosis* due to (1) tubular insufficiency without glomerular insufficiency, and (2) the Fanconi syndrome; (c) *idiopathic hypercalciuria*; and (d) *transient osteomalacia* following removal of a parathyroid adenoma.

For practical purposes, simple vitamin D deficiency is nonexistent in the United States. Elsewhere it responds well to the administration of vitamin D in small doses. In vitamin D-resistant osteomalacia (adults), or late rickets (growing children), massive doses of vitamin D are required. In the osteomalacia resulting from hypovitaminosis D due to steatorrhea, deficiencies of other fat-soluble vitamins (A, E, and K) must also be treated, Milkman's syndrome of "pseudofractures" or "multiple spontaneous idiopathic symmetrical fractures" (Looser Zones) is considered to be a manifestation of osteomalacia because of its characteristic radiologic (skeletal), biochemical, and histopathologic changes and its response to vitamin D therapy.[101-104] Albright classified osteomalacia as to degrees of severity as follows: (1) chemical osteomalacia with low phosphatase levels; (2) chemical osteomalacia with high phosphatase; (3) Milkman's syndrome of pseudofractures with an otherwise normal skeleton and chemical osteomalacia; and (4) advanced osteomalacia with generalized skeletal involvement.

Mode of Action of Vitamin D[101-104]

The administration of vitamin D results in a sequence of events which may be explained as follows:

(1) Fecal calcium and phosphorus excretion are lowered.

(2) The decrease in fecal phosphorus excretion is secondary to the decrease in fecal calcium excretion.

(3) The decreased fecal calcium excretion results from increased calcium absorption from the bowel.

(4) Increased calcium absorption explains the rising serum calcium and increased urinary calcium only in patients with osteomalacia.

(5) The rise in serum phosphorus levels following administration of vitamin D in osteomalacia is not due to increased phosphorus absorption but to decreased parathyroid activity resulting from increased calcium absorption.

(6) An independent second action of vitamin D is to cause an increased urinary phosphate excretion. It is by this mechanism that decalcification results from large doses of vitamin D and that it causes elevation of serum calcium in normal and hypoparathyroid individuals. Thus in the presence of normal parathyroid function, the action of vitamin D in increasing calcium absorption may result in decreased parathyroid activity and thereby neutralize the phosphaturic effect.

Dihydrotachysterol (AT10) acts similarly but exerts a greater effect on phosphorus excretion than on calcium absorption. Thus, while dihydrotachysterol is the therapeutic agent of choice in hypoparathyroidism, vitamin D is preferred in the treatment of osteomalacia.

Insensitivity to vitamin D_2 (calciferol, viosterol, irradiated ergosterol) has been reported in patients with chronic tetany who were capable of responding to AT10 and vitamin D_3 (activated 7-dehydrocholesterol).[105–106] When the form of vitamin D was changed, all its actions were immediately manifest—improved absorption of calcium from the bowel, decreased renal threshhold for calcium, raised plasma calcium level, and fall of plasma phosphorus level. Such drug resistance may have some bearing on instances of vitamin D-resistant osteomalacia of varied causes.

The osteomalacia of steatorrhea is due to a combination of failure to absorb fat-soluble vitamin D, failure to absorb calcium excreted with fecal fat in the form of calcium soaps, and probably also a direct failure of calcium absorption from the bowel. Large doses (50,000 units/day) of vitamin D together with large doses of oral calcium (in the form of calcium lactate 15–30 g/day) does effect slow improvement of the osteomalacia.[107–109]

Vitamin D Intoxication

The signs of vitamin D intoxication have been extensively reviewed.[110–111] Manifestations involving many systems include: (1) general—weakness, fatigue, weight loss; (2) gastrointestinal—nausea, vomiting, diarrhea, abdominal cramps; (3) neurologic—headache, parethesias, vertigo; (4) psychiatric—mental symptoms, depression, psychosis, stupor; (5) hematologic—normocytic, normochromic anemia; (6) urologic—albuminuria with microscopic hematuria, casts, frequency, nocturia, and diminished ability to concentrate urine; (7) ophthalmologic—band keratitis; (8) biochemical—elevation of serum calcium, phosphorus, and blood urea nitrogen, normal or decreased alkaline phosphatase; (9) roentgenologic—diffuse demineralization of bones, periarticular soft tissue calcification; (10) pathologic—metastatic calcifications involving kidney, stomach, lung, blood vessels, heart, thyroid, pancreas, and periarticular soft tissues; metastatic calcium cysts and band keratitis are particularly emphasized.

The Fanconi Syndrome

Familial renal rickets, described by Fanconi in 1931,[112] and characterized by osteomalacia, hypophosphatemia, renal glycosuria, and aminoaciduria, has recently been the subject of a number of excellent reviews.[113–115] It has been suggested that it is a variant of a larger group of disorders or defects in various renal tubular functions, including reabsorption of water, glucose, amino acids, phosphate, bicarbonate, and potassium, and that such defects may be total or may exist in varying combinations. Thus we see nephrogenic diabetes insipidus with failure of water reabsorption, renal glycosuria with failure of glucose reabsorption, primary renal amino aciduria in Wilson's disease and cystinuria, vitamin D-resistant rickets with faulty phosphate reabsorption, and hyperchloremic acidosis or renal tubular acidosis, with failure of bicarbonate reabsorption. Fanconi used the term "phosphate diabetes" to include true phosphate diabetes (dominantly inherited), vitamin D-resistant rickets with hypophosphatemia, and the Debré-deToni-Fanconi syndrome characterized by the association of phosphate diabetes, chronic aminoaciduria and glycosuria. All probably result from an impairment of phosphatase and phosphorylase enzyme systems involved

in the reabsorptive mechanisms of the renal tubules, probably in the proximal segment.[113–115]

The principal abnormalities which have been noted in the Fanconi syndrome are (1) high renal clearance of phosphate, low concentration of inorganic phosphate in serum, and rickets or osteomalacia; (2) high renal clearance of glucose with glycosuria but normal glucose tolerance; (3) increased renal excretion of several amino acids and ammonia and increased titratable acidity of urine. Of the urinary organic acids, 82 per cent consist of amino acids, 11 per cent of lactic acid and 7 per cent of beta-hydroxybutyric acid. In several cases the disordered amino acid metabolism was reflected in cystine deposits in the reticuloendothelial system; (4) hyperchloremic acidosis due to faulty bicarbonate reabsorption; and (5) normal levels of serum calcium and blood urea nitrogen. In addition, polyuria unrelated to osmotic diuresis has been attributed to defective reabsorption of water. Occasionally hypokalemia results from excessive potassium excretion. Impairment of hepatic glycogenolysis with ketonuria as a manifestation of a general impairment of carbohydrate metabolism, has also been observed in association with chronic aminoaciduria, renal glycosuria, and phosphate diabetes.

Inheritance of phosphate diabetes with vitamin D—resistant rickets involves dominant traits, and the Fanconi syndrome a single recessive trait. Renal glycosuria, phosphaturia, and aminoaciduria have been produced experimentally in young rats by injections of maleic acid.[116] This suggested a specific interference of maleic acid with the tubular reabsorption of these substances.

The observation of hyperuricosuria accompanying the hyperphosphaturia is of interest in connection with other reports of a relationship of the tubular reabsorption of urate and phosphate.[26] The morphologic observation of degenerative changes in the proximal renal tubules, and the reported absence of intracellular phosphatase in the proximal tubules have led to speculation that defective phosphorylation may be responsible for the faulty reabsorption. However, many patients with chronic aminoaciduria also have disturbances in intermediary metabolism of amino acids. Twenty per cent of the cases have been associated with cirrhosis, presumably on the basis of prolonged loss of essential amino acids, as occurs in Wilson's disease.

Evidence that vitamin D increases the activity of alkaline phosphatase obtained from bone and kidney, together with observations on the efficacy of vitamin D in the treatment of vitamin D-resistant rickets, has encouraged the use of large doses of vitamin D in the treatment of the Fanconi syndrome. Doses ranging to 400,000 units/day of vitamin D for 30 days have resulted in significant decreases in urinary ammonia, amino acid, and glucose excretion, and positive phosphorus balance, with normal plasma phosphate, bicarbonate, and chloride. The biochemical improvement was accompanied by symptomatic improvement, relief of bone pain and of weakness.[117] Other measures have been directed toward improvement of mineral balance with high calcium and phosphorus intake, alkalinizing therapy using Shohl's citric acid–sodium citrate solution, and methyl testosterone (25 mg orally per day), which increases retention of calcium, phosphorus, and nitrogen, and diminishes ammonia and amino-nitrogen excretion in the urine.

The Fanconi syndrome is reportedly rare in adults. However, the question has been raised whether many of the cases formerly described as Milkman's syndrome or glycosuric rickets may not have represented similar renal tubular defects.

The Fanconi syndrome differs from tubular acidosis entirely, in that in the Fanconi syndrome the acidosis is due to an excess of organic acids being presented to the kidneys for excretion, while in tubular acidosis the acidosis is due to decreased ability of the kidneys to make ammonia and to excrete an acid urine. Thus the Fanconi syndrome is characterized by increased organic acids, increased ammonia, and increased titratable acidity in the urine, while in renal acidosis the urinary organic acids are normal, ammonia is decreased, and titratable acidity of the urine is decreased. In both the urinary calcium excretion is increased.[101]

Evidence has been presented to suggest that the osteomalacia of the Fanconi syndrome is secondary to excessive urinary excretion of phosphorus, as a result of the specific defect in its tubular reabsorption, rather than to malnutrition, excessive primary urinary loss of calcium, or disordered organic acid metabolism. Thus, among the causes of osteomalacia may be listed decreased calcium absorption, increased calcium loss, decreased phosphorus absorption, and increased phosphate loss (the latter exemplified by the Fanconi syndrome).[118] Thus resistance of response to vitamin D therapy in the Fanconi syndrome may be attributed to the effect of vitamin D on increased urinary phosphate excretion, although it increases calcium retention.

Renal Tubular Acidosis

A rare variety of "renal rickets" has been designated variously as nephrocalcinosis infantum with hyperchloremic acidosis, nephrocalcinosis with rickets and dwarfism, chronic acidosis with late rickets, idiopathic renal acidosis, and renal acidosis resulting from tubular insufficiency-without-glomerular insufficiency.[119–121] Its essential feature is an inability of the kidneys to produce acid urine. Despite copious alkaline urine of fixed specific gravity, a systemic acidosis results from loss of fixed base (used in excretion of acid metabolites), with compensatory decrease in plasma bicarbonate and phosphate, and increase in plasma chloride concentrations. Urinary output of ammonia is decreased, and losses of body sodium, potassium, and calcium are large. In consequence, a low serum calcium level leads to development of rickets with multiple fractures, bony deformities, and compensatory parathyroid gland hyperplasia, presumably thereby accounting for the hypophosphatemia. Loss of potassium frequently leads to severe muscular weakness and even hypokalemic crises with paralysis. A frequently fatal variety has been reported in infants; in older children and adults the course is more prolonged. Nephrolithiasis and nephrocalcinosis are very frequent, presumably as secondary phenomena due to diminished solubility of calcium salts in alkaline urine. Polyuria and polydypsia are common; in fact, water and electrolyte balance are so precarious that a minor episode of vomiting or loss or restriction of fluids may precipitate a crisis of dehydration or hypokalemia. Recently deToni observed the association of renal acidosis with a syndrome of dwarfism, obesity, and hypogonadism.[122] Albright[101] viewed the sequence of events in renal acidosis as follows: (a) renal tubular insufficiency; (b) decreased ability to make ammonia and to excrete acid urine; (c) demand for calcium as a base; (d) hypercalciuria; (e) tendency to hypocalcemia; (f) parathyroid hyperplasia; (g) hypophosphatemia; (h) failure to deposit calcium phosphate salts in the osteoid; (i) osteomalacia; (j) hyperkaliuria and its manifestations of hypokalemia; and (k) high serum chloride and low CO_2 content.

The urinary excretion of citrate was practically absent in an infant with congenital renal tubular acidosis, persistent even after correction of acidosis. The similarity was noted, in elevated serum chloride, decreased bicarbonate concentrations, and fixation of urinary pH at 7 or above, between this syndrome and administration of a carbonic anhydrase inhibitor (Diamox®). Thus were prompted studies which demonstrated precipitation of calcium in the kidney in the presence of low urinary citrate concentrations.[39]

The etiology has been ascribed to chronic pyelonephritis, sulfanilamide toxicity with poisoning of the carbonic anhydrase system of the kidney, renal tubular injury of chronic potassium deficiency, or a congenital defect in the renal tubular mechanisms for reabsorption of bicarbonate. Its occurrence in infants and in twins and its familial incidence have suggested a congenital disorder.

Pathologic data are sparse. Of particular interest is the observation of vacuolization of the epithelium lining proximal convoluted tubules of the kidneys.* Alterations of the distal nephron (where acidification of urine, reabsorption of chloride, and formation of ammonia occur) consisted of fibrosis which could have occurred secondary to calculus formation.[123]

* See the paper by Conn, this issue.—Ed.

Therapy has been directed toward supplying the patients with base to conserve body base stores, by giving alkalinizing salts such as Shohl's mixture, sodium citrate, potassium citrate, and sodium bicarbonate in total dosage ranging from 2 to 8 g three times a day. In infants treated with sufficient alkali, the prognosis is said to be good.[120] In addition, some have recommended the use of large doses of calciferol and a high calcium diet, to heal the rickets.[101] The dangers of inducing further renal lithiasis and nephrocalcinosis have led some to confine therapy to alkalinizing salts alone. The danger of administering sulfonamides has been emphasized, since they, like Diamox®, inhibit the carbonic anhydrase system which normally plays a role in acidification of urine.[119]

The differentiation of renal tubular acidosis from renal rickets with osteitis fibrosa is made on the following points with regard to renal rickets: (1) the bone disease is osteitis fibrosa and not rickets; (2) there is advanced glomerular as well as tubular insufficiency; (3) despite accompanying parathyroid hyperplasia, the serum phosphorus is high rather than low.[101]

Hypophosphatasia

A recently recognized form of rickets, characterized by a specific deficiency of tissue and serum alkaline phosphatase and defective calcification of bone matrix, has been designated as hypophosphatasia.[124–125]

The condition has been reported in infants several weeks to several months old with failure to thrive and skeletal tenderness. Rachitic bone lesions and diminished serum alkaline phosphatase activity fail to respond to treatment with vitamin D. The bone lesions are indistinguishable from those of vitamin D deficiency rickets, showing grossly irregular maturation of cartilage with lack of calcification. In contradistinction to rickets, however, hypercalcemia has been observed. In most instances, the serum phosphorous level has been normal. Severe renal lesions have not been present except for functional depression consequent to hypercalcemia. Associated abnormalities have included premature loss of teeth, premature closure of cranial sutures, craniostosis, blindness, deformities, and dwarfism.

The observation of the presence of an abnormal phosphate monoester, phosphoethanolamine, in both serum and urine of patients with hypophosphatasia has given rise to speculation regarding pathogenesis. It has been suggested that phosphoethanolamine accumulation in blood and urine, in the absence of phosphatase enzyme, may represent the natural substrate for skeletal alkaline phosphatase, or one in some way related to it. A low concentration of the same material in the urine of the father of a child with hypophosphatasia suggests that hereditary factors are operative.

Familial Hyperphosphatemic Osteopathy

A rare form of familial "renal rickets" has been characterized by hyperphosphatemia, hypophosphatasia (alkaline phosphatase less than 1 Bodansky unit), and rachitic skeletal changes in the face of relatively normal renal function.[126] In addition, hypercalcemia, hypercalciuria, and hyperphosphaturia were present, attributed to secondary hyperparathyroidism. Roentgenologically, there was increased density of metaphyses about the knees and rarefaction of long bones. Renal clearance studies demonstrated excessive tubular reabsorption of phosphate, which could be depressed by administration of para-aminohippurate or probenecid. The condition was characterized as a "familial nephrogenic osteopathy" with secondary hyperparathyroidism, and mild depression of renal excretory function consequent to hypercalciuria. It has been suggested that such a pathogenetic mechanism could explain some of the idiopathic nephrocalcinoses.

Chronic Hypercalcemia Combined with Hyperphosphatemia, Hyperazotemia, osteosclerosis, and Dwarfism.

Fanconi[115] has described a syndrome in a 20-month old child, consisting of marked physical and mental retardation, symptoms attributed to hypercalcemia, hyperphosphatemia, azotemia, chronic acidosis, hypercholesterolemia, slight hyperglobulinemia, high erythrocyte sedimentation rate, and marked

eosinophilia. Albuminuria, intermittent microscopic hematuria, azotemia, and low clearance of inulin and urea, all suggested a nephropathy, probably a glomerular lesion. Urine was acid and ammonia excretion normal. There was massive hypercalciuria and hyperphosphaturia. Radiologically, there was marked cranial hyperostosis and increased density of nearly all the skeleton. The renal cortex showed small calcifications. The parathyroid was described as normal histologically, but following extirpation of two glands, the newly-formed bone was no longer osteosclerotic. The patient's father had massive osteosclerosis with hyperphosphatemia. A second case differed in having only slightly elevated serum phosphate.

Nephropathy Resulting from Osteoporosis of Immobilization

The effects of immobilization on the skeleton and calcium metabolism have now been well documented.[28–29] Even in the adult, the constant process of skeletal remodeling continues, so that osteoblastic new bone formation is in balance with osteoclastic bone resorption. It is presumed that during strict immobilization, the loss of mechanical stimulation to new bone matrix formation is lost and becomes overbalanced by undiminished bone resorption, leading to decalcification or osteoporosis of disuse. The speed of this process depends upon the degree of skeletal activity. Thus, during phases of rapid skeletal growth and great physical activity, as in growing children, the equilibrium is even more upset and bone calcium resorption even greater. Thus is explained the incidence of hypercalcemia in immobilized children and in adults with Paget's disease.

Albright and co-workers, in 1941, defined these relationships in a 14-year-old boy, immobilized from the waist down for five months for a fracture through a solitary cyst of the femur.[127] Hypercalcemia and hypercalciuria developed, and renal injury was manifested by albuminuria, lowered concentrating ability, and the presence of many calcium-phosphate casts. Following resumption of movement, serum calcium levels returned to normal and renal function improved. Subsequently, the same authors observed a similar phenomenon in adult patients with Paget's disease. A number of similar observations have been made.[128–131] Nephrocalcinosis and renal insufficiency are apparently more frequent in individuals (children) who develop hypercalcemia, and urinary lithiasis occurs more commonly in adults with hypercalciuria but normal serum calcium levels. Therapy consists of mobilization, forcing of fluids, and low calcium intake.

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Editorial

A Well-Deserved Tribute

If we need to be reminded of how young the laboratory science of nutrition really is, we should note that in April, 1956 a testimonial dinner was held in Washington, D. C., in honor of Dr. Robert R. Williams, who on his seventieth birthday stepped aside as chairman of the Williams-Waterman Fund for Combat of Dietary Diseases. For it was Dr. Williams who after many years of investigation and experimentation was able chemically to identify and synthesize thiamine—only twenty years ago![1]

What is perhaps most unique about this discovery is that Dr. Williams patented the steps in the synthesis of thiamine and turned the profits over to two organizations established to encourage further research (the Williams-Waterman Fund and Research Corporation). As Dr. Sebrell, who has succeeded Dr. Williams, says in this issue (pp. 582–84), more than six million dollars has been realized, all of which has generously and unselfishly gone into the war against human malnutrition.

Even more striking has been the recognition by Dr. Williams and his associates that achieving a laboratory triumph is hardly enough—the ultimate goal is the practical utilization of the discovery. Hence, he has devoted his untiring energy to bringing thiamine (which has dropped from about eight dollars to six cents a gram) to the millions in Asia and elsewhere who are sick and dying from the lack of it.

His work on grain (rice) enrichment is internationally known and his objectives can be stated as follows:

"Practical experience in trying to change dietary habits shows that unless cereal enrichment is made universal with respect to major staples, either by industry action or by government action, it may as well be abandoned. Any lesser action will have no more value than the simpler process of telling the people to take pills or to choose their food with scientific skill."[2]

That beriberi is still a major nutritional problem in many areas of the world is readily documented.[3] That it is slowly but surely disappearing from the earth is due in no small measure to a vigorous chemist who did not stop after synthesizing thiamine.

Two addresses, by Drs. Jolliffe and Sebrell, will be found in this issue. They indicate the significance of the man, his work, and, even more, the youthfulness of scientific clinical nutrition.

—S. O. WAIFE, M.D.

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Presentation of Testimonial Letters to Dr. Robert R. Williams at Testimonial Dinner, Mayflower Hotel, Washington, D. C., April 23, 1956

Mr. Chairman, Dr. and Mrs. Williams, Ladies and Gentlemen:

It is my very signal honor and, I must add, indeed my pleasure, to have been designated to present to you, Bob, this book of letters, written to you by about a hundred of your friends and colleagues. These letters express sentiments of endearment, admiration, and respect that many, if not most, people find themselves too shy or embarrassed to say to you face to face; they can, however, express their true feelings in a letter or on public occasions such as this.

These letters, Bob, are mostly from persons from this country, but they are also from friends in Cuba, Puerto Rico, and the Philippines. Also, Bob, a very large proportion are from people who address you familiarly as R. R.—or Robert—or, more frequently as just plain Bob.

All of these letters contain expressions of respect and admiration for you as a man; as a trusted and honored friend; as a great scientist whose synthesis of thiamine can bring naught but good to the human race; and as a wise administrator of the funds accruing from the proceeds of your invention. All of these sentiments are repeated over and over again in these letters—and they must be common knowledge by now to all of us here.

But these letters say more than that. So that all of us here can share with you some of these expressions, I shall read excerpts from some of them.

One of your admirers says: "You share with such men as Pasteur, Dale, Fleming, and Waksman the glory of advancing knowledge in fields which can never bring anything but blessings to the human race."

Another says: "Your achievement has meant health and life to many millions who, otherwise, would have been sickly and died young. Hundreds of millions yet will benefit, thanks not only to your initial great achievement, but to your great and successful efforts to bring it to them. The billion people in Asia, half mankind, will learn that it is not man's inexorable fate to be sickly and to die young and that he can control nature and his destiny, that he can oppose voodoo with knowledge and reason, and that science can prevail if he will accept science."

The establishment of the Williams-Waterman Fund from the proceeds of your synthesis of thiamine was in itself a signal achievement and example; this has been recorded in the annual reports of the Fund, indicating that up to now some 230 grants-in-aid, amounting to about two and one-half millions of dollars, have already been used to advance our rolling frontier of nutritional and scientific knowledge. In these reports, however, little mention is made of the numbers of young men and women who have been trained as a by-product of these grants. Many of them now occupy positions of responsibility and influence in universities and research centers.

In this respect, one of your admirers says: "Establishment of the Williams-Waterman Fund made possible many advances in nutrition knowledge, by providing for the training of many young men and women in scientific pursuits."

Another notes that grants-in-aid from the Williams-Waterman Fund to a single laboratory either initially trained or advanced the training of a group of young men and women, five of whom are now full Professors, with a supporting group of Associate Professors, Assistant Professors and Instructors. One is a Foundation Director; one is Director of a State Bureau of Nutrition; one is a Director of one of the National Institutes of Health; one is a Manager of Clinical Research for a large pharmaceutical company. How often this has been repeated by recipients of your funds I do not know. But in your report summing up the activities of your Fund while under your direction, may I suggest that they, too, be recorded. From these letters they must be numerous, indeed.

Just one more quote:

"I am the third child of four children. My elders before me both died in infancy—Mother said they were victims of 'taon' (infantile berberi). Mother had her first child at the age of sixteen; she was nineteen when I was born. And the year was 1919. Tikitiki extract which the Philippine Bureau of Science put out after your efforts wrought its 'miracle' on me . . . after I had developed paralysis of my lower extremities, the residual effects of which often bother me to this day.

"I write this in behalf of my Mother who, without knowing it at the time, owes her first live child to your work. It is no twist of fate that I have with zeal joined the fight against beriberi, a fact which I reveal for the first time. Whenever Mother repeats the tragedy of my elders she reiterates the anguish of millions of other mothers."

So, Bob, I present to you this bound book of letters which contains expressions of ad

miration and of respect from a mere hundred of the millions of persons who have already benefited from your work. It is only a slight token of the great admiration we all feel for you as a man; as a scientist; and as a friend.

—NORMAN JOLLIFFE, M.D., Director
Bureau of Nutrition, New York City

Tribute to Dr. Robert R. Williams

It is truly a great honor and a rare privilege that has been given to me this evening, to pay tribute to an old friend and fellow worker who has not only accomplished great things in science but whose life and ideals have been a great inspiration to those around him. To know him is not only to admire him but to respect and to love him. There are many men who accomplish great things in research, but it is a rare combination that is found in Bob Williams of research ability, coupled with the determination and drive to follow up his research accomplishments with their application for the lasting benefit of mankind. His life really has consisted of several careers at the same time, but running through it you can see the path which led to the attainment of that rare satisfaction that so few men have the opportunity to experience—that of seeing the results of their work improve the lot of much of mankind.

Dr. Williams was born in Nellore, India, in 1886, the son of a Baptist missionary. It was undoubtedly the experiences of his boyhood in the missionary compound that did much to interest him in assisting the malnourished throughout the world. His ability to see and record accurately, as well as his human touch, are illustrated by his letters, treasured by his family and friends, which were written during his visit to India in 1950. I would like to read you a few sentences from the one he wrote when he revisited his birthplace at Nellore:

"Across the road the big banyan tree of our childhood years is gone; it died only a few months ago and leaves a great bare patch. . . . I stepped the distance off and found the branch of the parent tree could not have been less than 120 feet, probably more nearly 150 feet. I've told so many lies about it I wanted to check up. It could not have been as much as 200 feet without touching both our bungalow and the seminary building. . . .

"Our old garden is still surrounded by a wall 4 feet high but is broken in spots just from age. . . . Now the cactus hedges which used to surround the compound have been killed off by the cochineal bug which the government brought in for that purpose years ago. There is simply no cactus of the once common type with 'leaves' the size of a man's hand in all of south India. This is a great blessing as cactus was spreading everywhere and formed a great cover for the pest of cobras as we all remember how we used to see them by the dozen in the hedges. However, the loss of the cactus helps permit cattle, buffaloes and goats to wander over the compound and people, vehicles, etc., have made traffic lanes across it. . . . On this account, i.e., the cattle, the baptismal tank or pond north of the compound has been almost abandoned. By the way, I used to think of the tank (as all artificial ponds are called) as being miles from our bungalow but it is really not more than a half mile or so."

Dr. Williams' family brought him back to the United States when he was 10 years old, but as soon as he got his degree in chemistry from the University of Chicago he returned to the Orient by accepting a position in the Philippines where he came in contact with Dr. Edward B. Vedder of the U. S. Army Medical Corps. Vedder was much interested in beriberi and by substituting unpolished for polished rice eliminated beriberi from the Philippine scouts. Williams, working at the Philippine Bureau of Science from 1908 to 1912, tackled with Vedder the problem of the chemical identification of the factor in rice polishings which accounted for the relief of

beriberi. Williams quickly and without too much difficulty made concentrates from rice polishings which in small doses he saw relieve the severe symptoms of beriberi in infants. Thus he was started on the problem which he never gave up until he solved it more than 20 years later. It is of interest to note that his first paper from the Philippines, published in 1911, is entitled "Economic Possibilities of Mangrove Swamps," and the second, published in 1912, is entitled "Contribution to the Etiology of Beriberi," a really prophetic title which he could have continued to use for his entire career.

He returned to the United States in 1915 for work with the Department of Agriculture in Washington, where he continued to work on the problem until World War I carried him off into the Chemical Warfare Service, where he worked on lewisite and "dope" for airplane wings. In 1919 he began his work on developing better insulation for submarine cables and he soon developed an improved rubber insulation; this work led him into textiles, paper, paper condensers, lead covered cables, textile insulated wires, decay problems in telephone poles, and so many problems of value to the telephone business that by 1925 he was appointed chemical director of the Bell Telephone Laboratories. The successes he attained in this field and the load of work that he carried would have more than filled the time and absorbed all of the energies of most men, but Williams still had in his mind what it would mean to the world if he could only determine what it was in rice polishings that cured beriberi. So while he spent full time on the chemical problems of the telephone industry, all of his spare time went into chasing the elusive substance in rice polishings. For working space he converted his garage at home into a laboratory and filled it with pigeons for testing his concentrates. He obtained or made his own apparatus and spent all of his spare money, as well as his spare time. In 1925, the year he was made chemical director of the Bell Telephone Laboratories, he was also made a research associate in Teachers College of Columbia University, and here he was able to secure laboratory space and equipment and to gather around him a group of associates so that the problem could be pursued more vigorously and on an expanded scale. By 1933 an efficient method of isolating the vitamin had been finally worked out and he was able to obtain about 5 grams of vitamin from a ton of rice polishings. (It is interesting to note that in 1954 production in the United States was 244,760 lb.) Now they were faced with the problem of isolating the vitamin in quantity so that they could determine its chemical structure. The results were published in a series of now classical papers—19 in number—extending from 1935 to 1937, in which the various vitamin fragments are identified, its chemical structure determined, and its synthesis accomplished. At last the problem was solved over a span of 26 years from that first paper in 1911, and one might again say that here is an accomplishment of which any scientist could well be content—but not this man Williams. Because of his years with industry he was well aware of the need for patents in order to protect an invention and to ensure its proper development and use. He therefore patented each of the steps in his work and then persuaded his associates that they should not profit from this discovery which should be used to the fullest for human welfare.

The Research Corporation had been founded by Frederick Gardner Cottrell to meet just this situation and Williams turned the thiamine patents over to them, establishing the Williams-Waterman Fund in 1935 under an agreement by which two-thirds of the royalties are allocated to the Williams-Waterman Fund for the Combat of Dietary Diseases and one-third to the general funds of Research Corporation for the support of its regular grants program.

What this generous gift has meant is shown by the fact that since 1935 it has produced $6,145,000, with over $4,000,000 going to the Williams-Waterman Fund and $2,000,000 to general funds, while the price of thiamine has decreased from $7.98 a gram in 1936 to its present price of six cents a gram.

Now that the laboratory research problem was finished, Dr. Williams energetically under-

took to see not only that the royalties went to support more research in nutrition, but also by his personal efforts to see that neither time nor opportunity was lost in making the benefits of a plentiful supply of this essential nutrient widely available. He became a member of the Food and Nutrition Board of the National Research Council and chairman of its Committee on Cereals, a post he has held since 1940. He played a leading role in furthering the enrichment of bread in the United States. Finally, in 1946, he retired from the Bell Telephone Laboratories in order to give his full time to his nutrition work. Having assisted in and seen the health benefits of the enrichment of bread, flour, and corn meal in the United States, he carried his initiative and support back to the Philippines where he had first tackled the problem so many years before, and we find him supporting the studies which demonstrated the value of adding thiamine to white rice by assisting Dr. Salcedo and his group in showing that beriberi can be eradicated by this procedure. As a result, we can see the Philippines taking the leadership in Asia by enacting a law requiring the enrichment of white rice—a measure which, if enforced and extended to the large rice-eating areas of the world, could become one of the greatest contributions to health that the world has ever seen.

I would like to read you a few sentences from a letter which Dr. Salcedo wrote last month:

> "Please extend my very best wishes for continued good health and more success to Dr. R. R. Williams at the ceremonies on. . .April 23rd. I wish I could be present even only to shake his hand and express to him my personal and lasting gratitude for everything he has done to promote the health through good nutrition to our people. Undernourished millions the world over have benefited by his efforts. Countless co-workers, scientists and friends will always have him nearest to their hearts and uppermost in their minds for generations to come. I shall think of him more fondly. . .during the ensuing years."

Naturally, many honors have come to Dr. Williams. I will not try to enumerate them. Among numerous medals and citations are seven honorary degrees and they honor the donor in the giving. I am sure he will continue to receive others.

He has just passed his seventieth birthday and relinquished the chairmanship of his Williams-Waterman Fund, and, although he will not work regularly at the job, all of us who know him know that he will never cease to be concerned about the malnourished people of the world and that he will be contributing to their betterment as long as he lives.

It has been one of the great inspirations of my life to have had the opportunity to be associated with Dr. Williams in a small way for many years and to have been guided by his wisdom and experience on many occasions. I know that all of his associates will continue to look to him for advice and to call on him for help with the problems of human malnutrition which we know are so close to his heart.

In conclusion, to my mind Dr. Williams represents the best that religious freedom, intellectual freedom, and political freedom can produce. In the troubled times that we see ahead of us in the world, if this country can continue to produce men of Dr. Williams' caliber we have nothing to fear, and the world will be a better place for us all.

—WILLIAM H. SEBRELL, M.D.
Former Director,
National Institute of Health

Erratum

In the Letter to the Editor, "The Role of Amino Acids in Kwashiorkor," AMERICAN JOURNAL OF CLINICAL NUTRITION 4: 286, 1956, the sentence on the fifteenth and sixteenth lines from the bottom, second column, should have read: "There was loss of edema, regeneration of serum protein, and healing of skin lesions. . ."

Nutrition News

Nutrition Congress

The Fourth International Congress of Nutrition, organized under the auspices of the International Union of Nutrition, will be held in Paris, France, July 24–29, 1957.

The work of the Congress will be divided into the following sections: (1) The Influence of Nutrition on Lactation; (2) Nutrition and Reproduction; (3) Nutrition and the Skin; (4) Nutrition and Intestinal Bacteria; (5) Nutrition and Old Age; (6) all papers that do not fall within the above categories.

Papers should be addressed to: President, IV International Congress of Nutrition, 71 Boulevard Péreire, Paris, France.

World Medical Association

The tenth General Assembly of the World Medical Association will be held in Havana, Cuba, October 9–15, 1957. The scientific session will be devoted to cardiology and nutrition. Dr. Vincente Banet Pina, professor of surgery at the University of Havana, is chairman of the session. Communications should be addressed to Dr. Louis H. Bauer, secretary-general, 10 Columbus Circle, New York 19, New York

At this Assembly there will also be meetings of the Pan American Medical Association and the International Hospital Association.

Arteriosclerosis Group Meets

This year's meeting of the American Society for the Study of Arteriosclerosis will be held at the Palmer House, Chicago, on November 11 and 12. The program and abstracts of papers read will be published in the October 1956 issue of *Circulation*.

Public Health Association

The 84th annual meeting of the American Public Health Association and meetings of 40 related organizations will take place in Convention Hall, Atlantic City, November 12–16, 1956.

Highlights of the 81 sessions will include reports on: new food processing and preservation methods, including use of antibiotics, radiation and radioactive products; latest developments in fluoridation of water supplies to prevent tooth decay; experiences in recent outbreaks of milkborne paratyphoid B infections, encephalitis, and streptococcal disease.

Lipotropic Research Grants-in-Aid

The Lipotropic Research Foundation of New York will receive applications for grants-in-aid for 1957 until November 1, 1956, with special attention being given to clinical studies. A request for application forms, which should include a short statement describing professional affiliations and experience, may be addressed to the administrative secretary, Dr. L. Lipton, 26 Vark Street, Yonkers 1, New York.

Nutrition Briefs

BOTH small and very large doses of hydrocortisone cause sodium retention in adrenalectomized rats. Paradoxically, intermediate doses (50–500 μg/rat) cause an increased excretion of sodium.

D. H. P. Streeten, M. E. Pont, and J. W. Conn. *J. Lab. & Clin. Med.* 46: 729, 1955.

PANTOTHENIC acid, in its metabolically active form as coenzyme A, participates in synthesis of adrenal steroids. Experimental data demonstrate that this vitamin is necessary for steroidal production because coenzyme A acts in the condensation of two-carbon molecules.

A. B. Eisenstein. *J. Lab. & Clin. Med.* 46: 811, 1955.

TWO CASES of a unique hypochromic, normocytic anemia did not respond to iron, vitamin B_{12}, or folacin. A prompt response followed *oral* administration of crude liver extract.

D. L. Horrigan, R. M. Whittington, R. Weisman, Jr., and J. W. Harris. *J. Lab. & Clin. Med.* 46: 829, 1955.

HISTAMINE stimulates water and pepsinogen secretion through a cholinergic mechanism, but stimulates hydrochloric acid secretion through a carbonic anhydrase mechanism.

B. Hirschowitz and J. London. *J. Lab. & Clin. Med.* 46: 826, 1955.

SMALL daily doses of vitamin B_{12} precipitated and aggravated clinical manifestations of folic acid deficiency in two elderly people. Folic acid promptly reversed the process. This is additional evidence for a reciprocal relation between folic acid and vitamin B_{12}.

J. W. Harris. *J. Lab. & Clin. Med.* 46: 822, 1955.

THE PHOSPHORUS content of rachitic cartilage increases due to the influence of vitamin D preparatory to the onset of calcification.

J. G. Joshi and P. K. Dikshit. *Nature* 177: 625, 1956.

TURKEYS born of vitamin E-deficient hens have bilateral cataracts. In the embryo the lens protein forms but subsequently liquefies.

T. M. Ferguson, R. H. Rigdon, and J. R. Couch. *A. M. A. Arch. Ophthal.* 55: 346, 1956.

IN SCURVY the response to injury to the brain is similar to that seen elsewhere in the body, i.e., the reparative processes are less pronounced than in normals.

S. Sriramachari, C. L. Pirani, and W. Haymaker. *Am. J. Path.* 32: 131, 1956.

EXPERIMENTAL liver disease in rats (long-term CCl_4 poisoning) was associated with a urinary excretion of lower-than-normal amounts of citrovorum factor after folic acid loading. Impaired liver function was apparently responsible for the failure to convert folic acid to citrovorum factor, a task believed to be effected in large part by the liver.

V. Ferrari. *Acta vitaminol.* 9: 241, 1955.

THE POSSIBILITY of a synergism between vitamin B_6 and cortisone is suggested by results of a study in which phosphorylated vitamin B_6 and cortisone were administered to rats with experimental (formalin-induced) arthritis. The two agents combined appeared to be more effective than cortisone alone.

B. Gerocarni and C. Caldarera. *Acta vitaminol.* 9: 261, 1955.

IN LIVER disease, absorption of blood from the gastrointestinal tract produces an abnormally high concentration of blood ammonia.

C. Burnside, P. Young, H. C. Knowles, Jr., and L. Schiff. *J. Lab. & Clin. Med.* 46: 801, 1955.

Nutritional Quotes

Breast Best in Tropics

"Contrary to infant-feeding practice in other parts of the world, the introduction of semisolids during the first six months of infant life cannot be recommended in the sub-tropics and tropics because of the tremendous danger of gastroenteritis. Breast-feeding alone is the method of choice for the first six months."
—*Chron. World Health Org.* 9:217, 1955.

Abnormal Iron Requirements in Normal Infants

"It seems that during normal infancy the average requirement for iron per kg of body weight greatly exceeds that of the adult, and one normal infant's need for dietary iron may exceed that of another by as much as 300 per cent. To consider iron requirements in normal infants in terms of the average infant may fall far short of the requirements of a significant segment of the normal infant population."
—P. Sturgeon. *Report of the 19th Ross Pediatric Research Conference*, p. 49, 1956.

Minerals and Metals

"Of the dozen or more mineral elements which are known to be dietary essentials for man, only five or six are likely to be deficient in restricted diets. Of these, sodium, chlorine, and iodine should regularly be supplied by common salt and not in a vitamin-mineral mixture. As regards the various trace elements, such as copper, manganese, zinc, cobalt, and molybdenum, which are essential primarily in enzyme systems, there is lack of evidence that their addition as such to the human diet is needed under any conditions. It is agreed that this is a field in which studies are badly needed."
—L. A. Maynard. *Journal of the American Dietetic Association* 31: 332, 1955.

Antibiotic-Vitamin Combinations

"The efficacy of administration of antibiotic and vitamin combinations, as compared with antibiotics alone, in the therapy of specific infections has not been tested in controlled experiments. Until more information is available, it is impossible to state which vitamins if any, should be administered with which antibiotic in the treatment of a given infection."
—Grace A. Goldsmith. *New England J. Med.* 254: 171, 1956.

Diet vs. Lipotropic Agents in Cirrhosis

"There is no valid evidence that supplementing an adequate diet with choline, methionine, other lipotropic agents, or vitamins brings about more prompt or more complete recovery than might be accounted for by the diet alone. The conclusion is justified that patients with fatty cirrhosis of the liver receive optimal nutritional therapy if they are provided with adequate, well-balanced diets."
—G. J. Gabuzda. *J. A. M. A.* 160:969, 1956.

Nutrition and our Changing Population

"Within 25 years there will be, in the adult population, three special persons for every able-bodied worker. There will be: one physically handicapped, one chronically ill, one over 65 years old.

Nutrition can help every one of these groups to better and more useful lives."
—L. B. Pett, *Canad. Serv. Med. J.* 7: 198, 1956.

Decontamination of Food for Civilians

"One of the first problems following an attack with biological, chemical or nuclear weapons will be to provide safe food to the surviving population. The Public Health Service shares the responsibility for planning to meet this problem with the Department of Agriculture and the Food and Drug Administration. The Public Health Service area of planning includes the protection and sanitation of milk supplies and other foods in retail markets, restaurants, other public places, and in the home.

"Research needs fall into four principal categories: (a) rapid procedures to distinguish the nature of the contaminant; (b) means for preventing or eliminating contamination by biological and chemical aerosols and radioactive fallout; (c) practical decontamination procedures for foods; and (d) problems of sanitation and emergency storage of foods needed for mass feeding of displaced persons.

"Emergency decontamination of other essential items (food containers or packages, eating and drinking utensils, clothing and bedding) and of the person and the shelter area is also being studied. Under some conditions and for some items, routine cleansing with soapy water may be the most important phase of decontamination. Information will be obtained on the probable kinds, amount and persistence of contaminants, as well as the effectiveness of available decontaminants under emergency conditions."
—H. G. Hanson. *Pub. Health Rep.* 7: 189, 1956.

Malnutrition and Infection

"There is abundant evidence that infection intensifies poor nutrition. Clinicians practicing in areas in which malnutrition is common have frequently observed the precipitation of acute vitamin-deficiency disease, such as beriberi or pellagra, by an infectious process. Infections are often associated with anorexia, nausea, and vomiting, which limit nutrient intake. Loss of nutrients in the stool occurs when diarrhea accompanies infectious processes. Although supplementation with certain vitamins seems to be indicated in many of the situations just mentioned, there are no quantitative data on vitamin requirement under any of these conditions."

—Grace A. Goldsmith. *New England J. Med.* 254: 166, 1956.

Pyridoxine and X-Ray Sickness

"There is no supportive experimental evidence regarding the use of pyridoxine in postanesthetic nausea and vomiting and very little for its use in x-ray sickness. Rats treated with total body irradiation handle urea nitrogen in the same way whether vitamin B_6 is administered or withheld. However, there is a general belief that roentgen rays exert a damaging effect on many enzyme systems, especially those for which the B complex vitamins serve as coenzymes. If this is true, vitamin B_6 as well as other B complex vitamins might be helpful in reversing damaging effects."

—Richard W. Vilter. *J. A. M. A.* 159: 1213, 1955.

Income and Ignorance

"Surveys indicate that low-income groups also have less knowledge of nutrition and their deficiencies are partly chargeable to ignorance or indifference about the importance of a good diet. This is an important cause of poor dietary practices at all levels and serves to emphasize the fact that in this country where nutrients are in surplus supply and where knowledge can help greatly in obtaining a low-cost adequate diet, the most important step in correcting existing deficiencies is education."

—L. A. Maynard. *Journal of the American Dietetic Association* 31: 330, 1955.

Geriatric Malnutrition

"Malnutrition is one of the most difficult problems encountered in the chronically ill. Sometimes senile dementia is its root, at other times loneliness or neglect by the family. Dietary fears and fads result in malnutrition. We have found that many cancer patients admitted to the Holy Ghost Hospital gain weight during the first few weeks of hospitalization. This may be explained by a variety of factors. The nurses are solicitous and attentive to dietary wishes; the food is good and served in an appetizing way; and the surroundings are pleasant. Spiritual needs are catered to; pains and discomforts are skillfully palliated. All of these factors contribute toward better nutrition and are effective enough to bring about temporary weight gains even in the stubborn malnutrition of neoplastic disease."

—F. Homburger. *Geriatrics* 11: 171, 1956.

Practical Diet Therapy

The AMERICAN JOURNAL OF CLINICAL NUTRITION is pleased to announce the availability of a booklet entitled PRACTICAL DIET THERAPY. This is a collection of permanently useful articles which have appeared in the Diet Therapy section of this JOURNAL.

Starting, as all diet therapy must, with the concept of the *"normal" diet*, this guide goes on to discuss the various adaptations of the basic pattern to specific therapeutic aims. Included are papers on bland and liquid diets, high protein regimens, limitation of dietary cholesterol, the low purine diet, and sodium restriction. Other articles deal with diet in diabetes and the principles of geriatric nutrition. A special series of papers gives practical advice on diet in pregnancy, infant feeding, and the nutrition of preschool and school-age children. The special dietary problems and procedures involved in metabolic studies are also covered, and the discussion of correct dietary nomenclature is a "must" for anyone required to write diet prescriptions.

This collection of helpful reprints is priced at $2.00 per copy, and is obtainable from the publisher.

Reviews of Recent Books

Infant Nutrition in the Subtropics and Tropics (World Health Organization: Monograph Series No. 29), by D. B. Jelliffe, Geneva, 1955, pp. 237, $5.00.

This book was written for the World Health Organization after a tour of the Middle and Far East, the main object of which was to examine methods of infant feeding. The author has, however, extended his scope to include as far as possible information from all parts of the tropics and subtropics. He is very well fitted to do this, having worked in Africa and the West Indies before making this survey for WHO.

The book is divided into six chapters: the first is an account of the evolution of infant feeding in the Western world. This is followed by a description of infant feeding practices in tropical and subtropical countries. The third chapter is an analysis of the nutritional diseases of infants, and then come two chapters on the improvement of infant feeding and the prevention of kwashiorkor. The last section deals with nutrition education in Maternal and Child Health (MCH) Centers.

To the medical reader who is already familiar, at least in outline, with the nutritional problems of the tropics, the most important and interesting parts of the book are the first and the last. In the first chapter Dr. Jelliffe outlines what might be called his philosophy of infant feeding. His approach is at once scholarly and practical. His ideas are based on a great width of reading, in which very varied sources have been drawn upon—anthropological and historical as well as purely medical. The main point that emerges is that to wean a baby on the milk of animals such as the cow is an exceptional rather than a normal practice. This is a Western custom of comparatively recent origin, and is therefore by no means the necessary or sole solution to the problem of infant feeding in the tropics. The policy advocated for countries where there is no indigenous and widely available supply of animal milk is to prolong breast feeding for at least two years. In other words, the mother should be looked upon as a human cow, and therefore she must be fed accordingly.

The improvement of the baby's and of the mother's nutrition therefore goes together. Both are the concern of the Maternal and Child Health Center. In the last chapter, on the methods of nutrition education in these centers, the author stresses very strongly the importance of paying attention to local conditions and customs, and of enlisting the active cooperation of the mothers, instead of treating them as ignorant inferiors. Some interesting examples of successful techniques are given: for instance, in a Mexican village it was found that what the people particularly wanted was to be taught arithmetic; when this need was filled their confidence and cooperation were established—an indirect but none the less effective approach.

The description of the clinical aspects and prevention of infantile malnutrition in the tropics covers more conventional ground, but nevertheless Dr. Jelliffe manages to bring out a number of interesting points that need further investigation. It is surprising, for instance, to learn that rickets is extremely common in the countries of the Middle East. Much attention is given to nutritional anemia in infants; here, perhaps, the author lays too much stress on iron deficiency, and too little on deficiency of protein as a probable cause, although the work of Altmann is quoted.

Undue reliance is perhaps placed on published figures for amino acid requirements, which can only be rough approximations, and the best authorities are not cited. The figure Dr. Jelliffe quotes for the infant's protein requirement—3–4 g per kg body weight per day—is almost certainly too high, and may do harm by setting an impossible target.

These, however, are minor criticisms. This is a careful, stimulating, and well-balanced book. It should prove most useful to nonmedical as well as medical workers who are concerned with the important and urgent problem of infant nutrition in the tropics.

J. C. WATERLOW

The Biliary Tract, by Julian A. Sterling, The Williams and Wilkins Co., Baltimore, 1955, pp. 424, $10.00.

The author, who has had extensive clinical and investigative experience in problems dealing with the anatomy, physiology, and pathology of the biliary tract, has written this monograph by himself, with the exception of the chapter on anesthesia. The advantages of having a single author are evident in the uniformity of style of writing, the continuity, and the lack of duplication.

This monograph encompasses all phases of study of the biliary tract. It deals with anatomy, physiology, laboratory studies, and radiology, as well as the medical and surgical aspects of its diseases. Where possible, the author employs tables for statistical studies, analysis of laboratory data, and for differential diagnosis. These are well done and will be helpful to those who wish to seek out such information quickly. The illustrations are abundant and are frequently supplemented by anatomic sketches which help to clarify many details.

The author employs a terse, almost telegraphic, style of writing. Although this makes for ease of reading, in some instances it causes ambiguity or uncertainty as to the intended meaning. On controversial matters, Dr. Sterling quotes liberally from the theories or beliefs of authorities or investigators who hold opposing views. While such impartiality is commendable, this reviewer feels that the author should invoke his editorial prerogatives or at least indicate how his own experiences influence his thinking on a given subject. One might further suggest that additional simplification could be attained by allowing discarded theories to remain undisturbed.

All too often a medical text is obsolete by the time it reaches the reader, but in this respect Dr. Sterling is to be commended for the currency of his material. Such topics as drug-induced hepatitis (particularly that due to thorazine), biligraphin radiography, therapy of pancreatitis, and recent advances in surgery of the biliary tree are more than adequately covered.

The author is to be congratulated for providing students and clinicians with an excellent presentation of the subject matter which reads like a novel and yet is pithy and comprehensive. STANLEY H. LORBER

How to Reduce Surely and Safely, by H. Pollack with A. D. Morse, McGraw-Hill Book Co., Inc., New York, 1955, pp. 157, $2.95.

This book offers a sane, interesting, convincing presentation of the need for, and problems of, maintaining ideal body weight. It is keyed to the individual reader and should be a valuable adjunct to weight control programs. Although the major emphasis is in connection with safe and sane reducing, the last chapter is devoted to the problems of the underweight; furthermore, sections on assessing ideal weight, counting calories, and menu planning can be used equally effectively by the over- or underweight.

Technical aspects of energy needs, such as basal metabolism, radiation losses, caloric value of food, and costs of exercise, are treated in interesting, accurate, nontechnical language.

The reader will receive help in assessing the ideal weight for his sex, height, age, and activity. If weight reduction or gain is indicated by deviations of actual weight in excess of ±10 per cent of this ideal weight, menu patterns providing diets ranging from 800 to 3000 calories daily will be helpful. Other valuable aids are: a calorie counter (caloric value of individual servings of foods); a listing of 100-calorie portions of foods; a list of foods of *high fat* content; and recipes for low calorie desserts, salads, soups, and fruit punches with the actual calorie value of each listed.

The reviewer believes that this book could be recommended to persons wishing to gain or lose weight with full assurance that they should thereby gain the confidence that weight control is desirable and possible. The sections on the importance of good nutrition are convincing and valuable for readers of normal weight.

In future editions, it would be an improvement to list nude heights and weights (rather than height with shoes and weight, as ordinarily dressed) since clothing weight varies from season to season and height of heels in women's shoes is quite variable. The text recommends that persons undertaking active weight loss or gain should weigh weekly before breakfast and recommends in addition attention to maintenance of desirable weight at 25 years of age. Such a preventive program would be enhanced by regular use of scales within the home. JANICE M. SMITH

Transactions of the Fifth Meeting of the International Society of Geographical Pathology, Washington, D. C., September 6–11, 1954. S. Karger, Basel, 1955, pp. 385–950, Swiss francs, 67.60.

About two years ago, a unique conference was held in Washington, D. C. The International Society of Geographical Pathology met to consider the problems of cancer from a global viewpoint. In this multilingual book of more than 500 pages, experts from all over the world discuss epidemiologic and ecologic aspects of cancer of the stomach, liver, breast, uterus, and lung. Among the presentations are two of special interest to readers of the Journal: "Nutritional States as Causal Factors of Cancer" by Professor J. W. P. Davies of Kampala, Uganda, and "Nutritional States in the Causation of Primary Liver Cancer" by Dr. Charles Berman, South Africa.

Much of the book makes fascinating reading. The differences in incidence of new growths in different races and in different parts of the world have always been a curious mystery which investigators have felt may furnish a major clue to the riddle of cancer. These papers furnish the best available information on the subject today. This book will be both interesting and informative to workers in oncology, public health, epidemiology, and nutrition. S. O. WAIFE

Books received for review by the AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable those of special interest are selected, as space permits, for a more extensive review.

Tomorrow's Food (ed. 2), by J. Rorty and N. P. Norman, The Devin-Adair Co., New York, 1956, pp. 297, $3.95.

Infant Metabolism, World Health Organization, The Macmillan Co., New York, 1956, pp. 435, $8.00.

Hutchison's Food and the Principles of Dietetics (ed. 11), revised by V. H. Mottram and G. Graham, Edward Arnold (Publishers) Ltd., London, and Williams & Wilkins, Baltimore, 1956, pp. 630, $8.25.

A Pictorial History of Medicine, by O. L. Bettman, Charles C Thomas, Springfield, 1956, pp. 318 $9.50.

Alcoholism as a Medical Problem, edited by H. D. Kruse. Hoeber-Harper, New York, 1956, pp. 102, $3.00.

Abstracts of Current Literature

CHARLES R. SHUMAN, M.D., EDITOR

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MARTIN SILBERBERG, M.D., *St. Louis*
JANICE M. SMITH, PH.D., *Urbana*
JEREMIAH STAMLER, M.D., *Chicago*
BARNETT SURE, PH.D., *Fayetteville*
JOHN WATERLOW, M.D., *Kingston, Jamaica*

NIACIN REQUIREMENTS AND METABOLISM

A precise value for niacin requirement is difficult to define because of the formation of the vitamin by dietary tryptophan, a conversion requiring pyridoxine. Using pellagragenic diets, low in tryptophan, consisting of cereal products, a level of niacin intake of approximately 8 g has been proposed as adequate in two independent studies.

Studies of Niacin Requirements in Man. II. Requirement on Wheat and Corn Diets Low in Tryptophan. G. A. Goldsmith, H. L. Rosenthal, J. Gibbens, and W. G. Unglaub. *J. Nutrition* 56: 371, 1955.

The niacin requirement of humans can be determined only in relation to the tryptophan content of the diet, since it has been shown that the amino acid tryptophan is converted to niacin compounds in man as well as in many other species.

Three subjects were maintained for 90 to 105 days on a "wheat" diet which furnished approximately 5 mg of niacin and 200 mg of tryptophan daily. One subject developed typical niacin deficiency beginning 80 days after the diet was instituted, a second developed amenorrhea, herpes of the lip and slight redness of the tongue papillae, and a third showed lassitude and depression as the only clinical findings. In contrast to this, each of three subjects previously maintained on a "corn" diet of comparable niacin and tryptophan content showed the characteristic clinical picture of niacin deficiency after about 50 days of the experimental period. Excretion of N^1-methylnicotinamide decreased to lower levels within a shorter period of time, and tryptophan excretion was slightly lower during the corn than during the wheat regimen.

The time at which pellagra developed, and the severity of the deficiency, seemed to be related to the intake of niacin and tryptophan per unit of body size with both the "wheat" and "corn" diets. However, this relationship may not completely explain differences in clinical and laboratory findings between the two regimens. The low tryptophan content of corn may not be the sole explanation of the pellagragenic effect of this cereal. When the "corn" diet was supplemented with varying amounts of niacinamide, a significant increase in excretion of niacin metabolites occurred when the intake approximated 8 to 10 mg daily. These data suggest that with the "corn" diet, which furnishes 200 mg of tryptophan daily, body niacin stores approach adequacy when the diet supplies 8 to 10 mg of niacin.—B. SURE

Maize and Pellagra. R. Braude, S. K. Kon, K. G. Mitchell, and E. Kodicek. *Lancet* 1: 898, 1955.

Nicotinic acid in cereals such as maize, wheat, barley, rye, and rice is present in a bound form and does not appear to serve as a source of the vitamin for the nicotinic acid-deficient rat, chick, or pig. The nicotinic acid can be released by hydrolysis with 0.5 *N* NaOH, and the experiment described was designed to test the availability of the vitamin to pigs after treatment of maize with alkali. The nicotinic acid metabolism of the pig is similar to that of man.

Three groups of pigs had a nicotinic acid deficiency induced and were then allotted three different diets. Group 1 was kept on the deficient diet, Group 2 was given 6 mg of nicotinic acid daily in addition, and Group 3 was given a diet in which the milling fractions of maize had been hydrolyzed for 30 minutes with 0.5 *N* NaOH.

Group 1 pigs gained almost no weight during the experiment. The Group 2 pigs recovered from their induced deficiency and gained weight well, and Group 3

pigs also recovered, although they gained weight at a somewhat slower rate than those of Group 2.

It is concluded that the difference between the Group 3 and Group 1 pigs is determined by the hydrolysis of the maize making nicotinic acid available to the Group 3 pigs, although the possibility of another chemical change has not been excluded.

It is thought that since the daily requirements of nicotinic acid for man have been estimated on the basis of dietary intake, as much as half of it may be unavailable and the true requirements are probably 6–8 mg rather than 12 mg. Alkaline treatment of cereal is a possible method of "enrichment" of the foodstuff.—F. E. HYTTEN

Information concerning the adequacy of the diet in niacin or tryptophan-containing protein can be obtained from analyses of the urine for the metabolites of niacinamide. Further observations on the effects of disease, exercise, and nutritional factors upon niacin metabolism are accumulating by use of these methods.

Nicotinic Acid Metabolism in Humans. I. The Urinary Excretion of Nicotinic Acid and its Metabolic Derivatives on Four Levels of Dietary Intake. E. I. Frazier, M. E. Prather, and E. Hoene. *J. Nutrition* 56: 501, 1955.

The nicotinic acid metabolism of six freshman and sophomore college women on four levels of dietary intake of nicotinic acid and tryptophan was studied. On a control diet providing 11.3 mg of the vitamin and 885 mg of tryptophan, the average amount excreted by the six subjects as the vitamin and its two major metabolites, N^1-methylnicotinamide and pyridone, balanced the intake. When the dietary nicotinic acid of the control diet was increased to 14.3 mg with a concomitant increase in tryptophan, there was a slight increase (1.0 mg) in the total amount of the vitamin and its metabolic derivatives found in the urine. Following the 28-day control periods of study, a basal diet containing 7.2 mg of nicotinic acid and 600 mg of tryptophan was fed for 11 days. The average decrease in total excretion during this regime as compared with the immediately preceding control level of excretion was 3.04 mg. On the basal diet the total average excretion (expressed as nicotinic acid) was 128 per cent of the amount ingested. During the postbasal period with an increase to 16.3 mg intake, the excretion of nicotinic acid and N^1-methylnicotinamide returned to control levels, while the amount of pyridone exceeded the prebasal level.

With each increment in dietary nicotinic acid, approximately one-third of the increase was excreted as pyridone; on the other hand, a comparable decrease in the intake of the vitamin was reflected in decreased amounts of the vitamin and N^1-methylnicotinamide excreted as well as the pyridone. There was considerable variation in the metabolic performance among the 6 experimental subjects.

The significance of the findings in this study has been discussed in relation to "normal" nutrition with respect to the nutrients studied.—B. SURE

Excretion of N^1-Methylnicotinamide and the 6-Pyridone of N^1-Methylnicotinamide in Urine of Human Subjects. H. L. Rosenthal, G. A. Goldsmith, and H. P. Sarett. *Proc. Soc. Exper. Biol. & Med.* 84: 208 1953.

The major excretory metabolites of nicotinamide in human subjects are N^1-methylnicotinamide and the 6-pyridone of N^1-methylnicotinamide.

In the present study, adult human subjects were maintained on constant diets low in nicotinamide and tryptophan. On such diets, they excrete approximately 3 mg of N^1-methylnicotinamide and 5 mg of pyridone N^1-methylnicotinamide. In some of the patients, the excretion of N^1-methylnicotinamide and of pyridone N^1-methylnicotinamide, following graded doses of 10, 25, and 50 mg of nicotinamide, respectively, was studied in three control female subjects. This was also studied in two female subjects with pellagra. From the data obtained, it appeared that significant differences in excretion of the metabolites occurred in the pellagra patients as compared to the normals when 10 or 25 mg of nicotinamide were given. The differences were much less marked when 50 mg were administered.—L. W. KINSELL

The Urinary Excretion of Tryptophan by Human Subjects on Controlled Diets Varying in Levels and Sources of Protein. E. I. Frazier. *J. Nutrition* 53: 115, 1954.

The amounts of "free" and total tryptophan excreted per 24 hours by 12 young adult women maintained on diets varying in levels and sources of protein have been studied. The amounts of the conjugated forms in the urine were derived by difference.

On constant intakes of a control diet providing 9.8 g of protein and 885 mg of tryptophan over periods of from 14 to 21 days, the mean levels of excretion were 30.6, 10.8, and 19.8 mg per day for total, "free," and "bound" tryptophan, respectively.

The same subjects were fed a basal diet with total nitrogen intakes of from 7.10 to 8.42 g and tryptophan intakes of from 521 to 616 mg per day for 14 to 35 days. On this regimen there was a slight decrease in the average amount of the "bound" form excreted (from 19.8 to 15.5 mg per day), while the average amount of "free" tryptophan excreted was the same: namely, 10.8 mg per day on both control and basal dietary regimens.

There was no apparent relation between the amounts of total, "free," and "bound" tryptophan excreted and the source or amount of dietary nitrogen. Further, the amount of tryptophan excreted was not related to body weight, surface area, basal calories, or urine volume. The data presented indicate a selective reabsorption of this amino acid by the tubules from the glomerular filtrate.—B. SURE

In the study of niacin metabolism, the dog has provided a fairly satisfactory experimental subject. Other animals, such as the rat, have manifested wide fluctuations in tryptophan requirements. Some of the problems involved are discussed in the following report.

The Tryptophan Requirement of the Rat as Affected by Niacin and Level of Dietary Nitrogen. W. D. Salmon. *Arch. Biochem. & Biophys.* 51: 30, 1954.

Previous demonstrations of interrelationships between tryptophan and niacin have indicated the need for a restudy of the quantitative requirements of the rat for tryptophan. Three basic diets which contained 7 per cent casein and 40 per cent degerminated corn grits, 7 per cent casein and 7 per cent corn gluten meal, and 9 per cent casein, respectively, were used. The level of amino acids was controlled by altering the level of casein or by the addition of gelatin, casein hydrolyzate, tryptophan, or glycine. Data were obtained which showed that: (a) niacin has a marked effect upon the tryptophan requirement and efficiency of food utilization; (b) the growth-depressing effects of tryptophan-deficient proteins or hydrolysates are due to increased requirement for tryptophan in the presence of adequate niacin; and (c) the tryptophan requirement fluctuates with the level of dietary nitrogen.

Since the conversion of tryptophan to niacin is considered to be inefficient and uneconomic, the tryptophan-sparing effect of niacin is of great significance in practical nutrition. On the other hand, niacin did not correct the growth depression when the addition of tryptophan-deficient material was of sufficient magnitude. Under the latter condition, the growth depression could be corrected only by tryptophan. Niacin corrected the growth depression only when the additions were made to diets that contained a limited surplus of tryptophan above that needed for use as the amino acid *per se*. The primary effect of tryptophan-deficient materials was to decrease the efficiency of utilization of tryptophan and hence to increase the requirement of this amino acid.

The requirement of the rat for tryptophan does not seem to be a constant value. It increases as the level of dietary nitrogen increases. With adequate niacin in the diet, the tryptophan required for normal growth at a dietary protein level of 10.8 per cent was 0.13 per cent of the diet. When niacin was omitted from the diet, the tryptophan required for normal growth at a 10.8 per cent level of dietary protein increased to 0.19 per cent of the diet. Without supplementary niacin and with casein used as a source of tryptophan, the tryptophan requirement for normal growth was 0.30 per cent of the diet.

In also considering previous work which showed that gelatin decreases the availability of methionine and hence increases the requirement for this amino acid, it is suggested that the imbalance effect is a general phenomenon that will alter the requirement of any essential amino acid.—M. K. HORWITT

The drop in eosinophils and rise in blood sugar reported in the following abstracts suggest that epinephrine release may occur as a result of administration of large doses of niacin. Activation of adrenal steroid release may follow hyperepinephrinemia to sustain the effects observed.

Effect of Niacin and Nicotinamide on Leukocytes and Some Urinary Constituents. A. Hoffer. *Canad. M. A. J.* 74: 448, 1956.

The author has used nicotinic acid or its amide in large oral doses (3–10 g/day) for the treatment of acute schizophrenia. This vitamin has also been reported to counteract many psychologic and physiologic reactions of LSD (lysergic acid), to have anticonvulsant properties, etc. As a further study of its action, a group of healthy volunteers, ages 18 to 41 years, took large doses by mouth.

Nicotinic acid produced a fall in eosinophils within two hours: the neutrophils increased, the lymphocytes decreased slightly. The ratio of urinary uric acid to creatinine was decreased. The urine became more acid; potassium was retained, while sodium excretion was increased.

Nicotinamide produced an early lymphocytosis (at 2 hours) and a later (4 hours) eosinopenia and neutrophilia. In contrast to the acid, the ratio of uric acid to creatinine was increased, while urine acidity was decreased. Both potassium and sodium excretion were increased.

This paper also briefly discusses the similarities and differences between nicotinic acid (and amide) and cortisone, epinephrine, and norepinephrine. The author makes the interesting suggestion that large quantities of nicotinamide compete with norepinephrine for methyl groups, and that large quantities of the vitamin might be of value in conditions characterized by epinephrine overproduction.—S. O. WAIFE

Effects of Niacin and Niacinamide on Blood Sugar. G. N. Bera. *Am. J. Physiol.* 175: 296, 1953.

Hyperglycemia resulted when niacin and niacinamide were injected into fasted rabbits. The maximum blood sugar and niacin blood levels were reached at one hour after injection. The epinephrine content of the blood was also high at this same time. The authors conclude that niacin or its amide stimulates the secretion of epinephrine. This, in turn, causes hyperglycemia. The epinephrine content in the blood after niacin may explain the cardiac stimulation, vasoconstriction, and rise in blood pressure found in these animals.—M. J. OPPENHEIMER

Influence of Nicotinic Acid on Serum Cholesterol in Man. R. Altschul, A. Hoffer, and J. D. Stephen. *Arch. Biochem. & Biophys.* 54: 558, 1955.

Serum cholesterol was determined before and after oral doses of 1 g of nicotinic acid were administered to healthy young medical students and to patients with various diseases. The authors found that nicotinic

acid ingestion decreases serum cholesterol. All of the subjects who received the nicotinic acid showed the "flushing" reaction with "burning" sensations of the skin. Hypercholesterolemic levels are affected more than normal levels. Nicotinic acid amide had no definite influence on serum cholesterol levels of 20 healthy young medical students.—M. K. HORWITT

NUTRITIONAL PROBLEMS INVOLVING THE GASTROINTESTINAL TRACT

The unfavorable sequelae of gastric surgery are principally (a) nutritional failure and (b) the postgastrectomy "dumping" syndrome. The latter condition occurs infrequently and is characterized by weakness, tremulousness, sweating, palpitation, and distension. It may occur directly after meals or within one to two hours after eating. Diet therapy involves the use of foods which will delay gastric emptying, prevent rapid fluctuations in blood sugar, and avoid influx of water into the small intestine through osmotic attraction. The problem of nutritional failure is probably a combination of diminished appetite, reduced caloric intake, and decreased fat absorption.

Nutritional Problems following Gastric Resection: Fat and Protein Absorption. E. H. Ellison. *Surg. Clin. N. Am.* 35: 1683, 1955.

Impairment of digestion and absorption is an important late postoperative complication in patients undergoing gastric resection for peptic ulcer or carcinoma. Certain of these patients are incapacitated by the nutritional disturbances to the point where they have been described as "gastric cripples." To gain further information as to the incidence, etiology, management, and prevention of the nutritional problems following gastric resection, a continuing study has been in progress at the Ohio State University College of Medicine during the past four years.

Nitrogen and fat absorption were assessed in 16 patients with subtotal gastric resections performed one to 31 months previously for gastric or duodenal ulcer. The patients were given fixed diets which approximated what they were eating at home. Fat absorption was apparently impaired in the entire group of patients—the apparent average fat absorption was about 70 per cent, as contrasted with the usual normal of 90–95 per cent. It is Ellison's belief that this disturbance in fat absorption, continued for long periods of time, accounts for the observed weight loss of many of these patients. The quantitative aspects of these observations are limited by the shortness of the periods of balance study—3 days. While an overall approximation of the situation may be possible by the method employed, in any single instance the data so obtained may be misleading.

Ellison mentions that the data suggest an inverse relationship between the efficiency of fat absorption and the amount of stomach removed—but it should be pointed out that the postoperative weight patterns are at variance with the fat absorption figures. There were less nutritional disturbances when the stomach remnant was anastomosed to the duodenum rather than to the jejunum. This is in keeping with observations from several other clinics and is leading to a revival of the gastro-duodenal anastomosis technique.

Ten patients with total or near total gastric resection for malignant tumors were also studied in the period one to 31 months postoperatively. The average weight loss of this group of patients was 19.6 pounds; none had regained his preoperative weight. The apparent fat absorption average was about 67 per cent in the seven patients with total gastrectomy and about 80 per cent in the three patients with near total gastrectomy. Fecal nitrogen was about normal in the latter group, somewhat high in the former. Esophagoduodenostomy appeared to be the method of choice for re-establishment of intestinal tract continuity.—S. M. LEVENSON

The Efficiency of Digestion in Gastrectomized Patients. R. Nicolaysen and R. Ragård. *Scandinav. J. Clin. & Lab. Investigation* 7: 271, 1955.

This paper is a report of an approximately 14-day study of nitrogen balance and fat absorption in 15 patients in whom total gastrectomy had been performed for carcinoma some 3 to 43 months earlier. In addition, in 10 patients a part of the pancreas had been removed. All but one were ambulatory and were living at home before they were called in for the study. No signs of metastases were found at this time.

A weighed mixed diet averaging 1410 cal/day (range 840–2100) was fed. In all but six patients there was a distinctly negative nitrogen balance. Although about 88 per cent of the ingested fat was absorbed, there was evidence of reduced absorption.

As the authors indicate, the negative nitrogen balance was probably due to the inadequate caloric intake. The excess fecal fat plus the comparatively low intake of fat-soluble vitamins leads the authors to suggest that totally gastrectomized patients might benefit from fat-soluble vitamin supplementation. Presumably the intake resulted from an *ad libitum* diet, although this is not specifically stated, and nothing is said about weight changes.—S. O. WAIFE

The influence of emotions and behavioral patterns upon gastric secretory activity has received much attention. Studies on human subjects with gastric fistulae have provided a wealth of information in terms of which psychophysiologic reactions and disorders are more clearly comprehended.

Behavior and Gastric Secretion: The Study of an Infant with a Gastric Fistula. F. Reichsman, G. L. Engel, and H. L. Segal. *Am. J. Dis. Childhood* 90: 491, 1955 (Soc. Trans.).

Physiologic, behavioral, and psychologic observations were made on a 16-month-old infant with congenital atresia of the esophagus in whom a gastric fistula had

been established on the third day of life. Over five months, during which she was hospitalized on the pediatric service, the child was studied in 59 experiments, each lasting two to four hours. Behavioral observations were recorded in detailed protocols by the experimenter who aspirated the gastric contents, as well as by an investigator who observed through a one-way screen the child and her transactions with the experimenter. Approximately 600 specimens of gastric secretion were examined as to appearance, total volume, pH, concentration, and secretion rate of free and combined HCl, and concentration and rate of pepsin secretion. Only the secretion rates of total HCl were reported.

The mean rate of total HCl secretion (meq/min) during depression is less than one-half than that during irritation, contentment, and joy ($P<0.001$) and about one-fourth of the rate during rage ($P<0.001$). During rage, secretion is significantly higher than during all other affects at the 1 per cent or at the 0.1 per cent level, except for the comparison with irritation, which is significant at the 2 per cent level. There are no significant differences between the other affects.

Thus, at this level of development, the secretion of HCl by the stomach is well integrated into the total behavioral activity of this infant. Affective states, be they pleasurable or unpleasurable, which are expressive of active communication with the outside world, are associated with rising secretion rates of HCl. The affect of "depression," in which communication with the environment is reduced or almost completely absent, is associated with decrease or cessation of gastric secretion. The authors regard these data as providing experimental support of the psychoanalytic theory of the oral phase of development.—J. N. ETTELDORF

Observations on "Unexplained" Chronic Diarrhea in Early Childhood. D. G. Prugh and H. Shwachman. *Am. J. Dis. Childhood* 90: 496, 1955 (Soc. Trans).

In the course of studies of gastrointestinal disorders in infancy and childhood, a group of cases has been identified which show continuing diarrhea related to psychophysiologic disturbance in gastrointestinal function. Symptoms tend to appear after the first six months of life and to continue at least into the second or third year. These cases appear to be distinct from idiopathic celiac disease, without the gastrointestinal absorptive defect and the metabolic reverberations which characterize that illness. Localized structural change, as in prolonged ulcerative colitis, does not occur in these patients, and careful physical and laboratory studies reveal no local or systemic abnormalities of immediate etiologic significance. Dietary and other traditional methods of treatment have been of limited value in the management of this type of disturbance. Present studies indicate that diarrhea in this group of infants and small children tends to appear in settings of family crisis or in relation to exacerbations of emotional conflict on the part of parents, with associated changes in the handling of these children. Genetic and somatic factors, such as the pattern of inherited autonomic response to stress and incidental physical illness involving the gastrointestinal tract, appear to play a role in the predisposition to these disorders.

A group of 20 cases is presented, exhibiting diarrhea of the type described. Detailed observations are summarized regarding the type of predisposition in child and parents, the precipitating factors operating to disturb "emotional homeostasis," the nature of psychophysiologic derangements, and the family circumstances which appear to lead to perpetuation of these disorders. Charts are employed to indicate correlations between significant psychologic and physiologic data. A program of pediatric management, involving a supportive psychological approach, is described, which can lead to successful resolution of this symptom picture.—J. N. ETTELDORF

It is not generally appreciated that native proteins can be absorbed from the gastrointestinal tract with no essential molecular alteration or hydrolysis. That such absorption does occur has been clearly demonstrated and has now been quantitated. Sensitization to native proteins absorbed in higher concentration during or after diarrheal states or impaired utilization of such proteins may be of some clinical moment.

The Gastrointestinal Absorption of Unaltered Protein in Normal Infants and in Infants Recovering from Diarrhea. F. L. Gruskay and R. E. Cooke. *Pediatrics* 16: 763, 1955.

The authors review briefly the qualitative evidence that ingested native protein may be absorbed from the gastrointestinal tract and that the amount entering the blood stream may increase during gastrointestinal disorders. Data of a quantitative nature are lacking.

With an immunochemical technique, quantitative determinations of a serum concentration of egg albumin were made following the ingestion of 1 g/kg of albumin in normal infants and in infants recovering from diarrhea. This study was conducted in order to correlate gastrointestinal absorption of protein with possible sensitization.

In one to two hours after ingestion of egg albumin, demonstrable quantities were present in the serum of control children, ranging from 0.45 to 73 μg per ml of serum. The levels of albumin in the serum of infants recovering from diarrhea in the absence of hemoconcentration was significantly higher and ranged from 4 to 53 μg per ml of serum. In 7 or 8 infants who had demonstrated an increased absorption of egg albumin during diarrhea, there was a significant decrease in the concentration during the convalescent stage.

The elevated concentrations of native protein were attributed to three possible mechanisms: (1) reduced destruction, (2) decreased excretion, (3) increased absorption of unaltered protein. The authors feel that the latter is more likely. Schloss has suggested that

increased absorption is possible because of hyperemia. Others have suggested it is the result of decreased degradation of the protein. Godlowski has suggested an altered capacity of the lymphoid layer of the lamina propria of the intestine to immobilize protein transport.

These observations of an increased absorption of protein during diarrhea, although egg albumin is of smaller molecular size than casein or lactalbumin, indicate to the authors that milk products such as Nutramigen ® which are free of whole protein, should be preferred to cow's milk during the recovery phase of diarrhea—J. N. ETTELDORF

The availability of a dependable and simple test to demonstrate impairment of absorption by the small intestine would represent an important adjunct to the study of many nutritional disorders. Further clinical trials with the test described below are in order.

The *d*-Xylose Tolerance Test: A Measure of Intestinal Absorption in Normal and Dystrophic Infants. M. G. Wolfish, G. J. Hildick-Smith, J. H. Ebbs, M. L. Connell, and A. Sass-Kortsak. *Am. J. Dis. Childhood* 90: 609, 1955 (Soc. Trans.).

It has been shown that in adult malabsorption syndromes, the xylose tolerance test is a useful measure of absorption and has certain advantages over the customary glucose tolerance test. In the present study, the value of this test was explored in infants.

d-Xylose was given in a dose of 0.5 g/lb of body weight (1.1 g/kg), with a maximum dose of 25 g as a 10 per cent aqueous solution, in the fasting state. Blood levels of xylose were obtained at 0, 1, 2, and 5 hours after the test dose.

A group of 55 normal infants was studied to obtain the range of normal tolerance. The results obtained in this group were fairly consistent. The blood xylose levels rose to at least 30 mg per 100 ml within two hours; all except four rose over 35 mg per 100 ml.

These results were compared to those obtained in 40 infants suffering from dystrophy and suspected to have malabsorption. These included cases of celiac disease, fibrocystic disease, milk allergy, dystrophy following various infections, dystrophy due to insufficient nutrition, and dystrophy of unknown etiology.

Glucose and vitamin A tolerance tests were also performed on this group of dystrophic infants, either immediately preceding or following the xylose tolerance test. The results obtained by these three tests of absorption were compared. In a smaller group of patients the tolerance tests were repeated during the course of their illnesses, and changes in their tolerances were noted.

The xylose test was "flat" in celiac disease and in other conditions where malabsorption may be a factor. This test was consistently normal in conditions such as fibrocystic disease and dystrophy due to insufficient nutrition where malabsorption of monosaccharides is not part of the disturbance.

The results of glucose tolerance tests were much less uniform in these groups. It would appear that the xylose tolerance test is a useful tool in the study of malabsorption syndromes in infancy.—J. N. ETTELDORF

Diarrhoea Due to Phenolphthalein. J. M. French, R. Gaddie, and N. Smith. *Lancet* 1: 551, 1956.

Two cases of chronic diarrhea due to self-medication with phenolphthalein are described. In one of the cases fat absorption was impaired.

Both initially denied taking phenolphthalein, and the method of its detection is outlined. Attention is drawn to the possible importance of self-induced diarrhea as a clinical syndrome and a further cause of steatorrhea.—F. E. HYTTEN